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Section of Surgery

President—JOHN BRUCE, C.B.E., T.D., F.R.C.S.Ed.

[*November* 2, 1955]

DISCUSSION ON CARCINOMA OF THE THYROID

Dr. I. Doniach:

Ætiology of Thyroid Carcinoma

During the past eleven years the induction of benign and malignant thyroid tumours in laboratory rats has become an established procedure in experimental pathology. I propose to outline briefly the methods used and discuss their possible applications to the problem of human thyroid carcinoma. The subject has been recently reviewed by Bielschowsky (1955) and by Axelrad and Leblond (1955).

Spontaneous benign tumours occur in the elderly rat's thyroid but are rare. Swiss workers noted during the period 1910 to 1930 that like humans, laboratory rats in endemic goitre districts developed goitres which often contained adenomas and very occasionally carcinomas. Controlled experiments on rats have since confirmed the goitrogenic action of iodine deficiency. A prolonged iodine-deficient diet leads to the development of adenomas after ten months and histological changes suggestive of malignancy after fifteen or more months (Axelrad and Leblond, 1955). The life span of the laboratory rat is about three years. Prolonged treatment with goitrogens, brassica seed (cabbage, mustard and turnip), thiourea, thiouracil and derivatives in the diet produces adenomas after eight months and carcinomas—7 in 13 rats in one experiment by Purves and Griesbach (1947)—after twenty months. Bielschowsky (1944, 1945) found the process considerably speeded up by the addition of the carcinogen 2-acetylaminofluorine (A.A.F.) to the diet given simultaneously with the goitrogen or as a separate pre-treatment. Pre-treatment with A.A.F. for fifteen weeks led to the development of multiple thyroid adenomas in ten weeks of goitrogen treatment. Bielschowsky (1949) also demonstrated the development of adenomas in the residual hypertrophied isthmus of thyroids in which both lateral lobes had been removed thirteen to twenty-five weeks previously in rats given A.A.F. but no chemical goitrogen. Adenomas were found fifteen months after the administration of 30 μC ^{131}I (Doniach, 1950) a not obviously destructive radiation dose to the thyroid, equivalent to a mean of a few thousand roentgens and comparable to that given in the treatment of Graves' disease. When a dose of 30 μC ^{131}I was followed by methyl-thiouracil maintained for twelve to fifteen months, adenomas were much increased in number and 5 thyroid carcinomas were found in 20 treated rats (Doniach, 1953). 7 thyroid carcinomas developed in 25 rats given 400 μC ^{131}I one and a half to two years previously (Goldberg and Chaikoff, 1952) and no other treatment. This is a very destructive dose giving a mean irradiation to the thyroid equivalent to 150,000 or more roentgens.

The common factor in the above experiments was a maintained thyroid hyperplasia due to a prolonged raised output of pituitary thyrotrophic hormone (T.S.H.). The relevant conditions which are considered to lead to a maintained rise in T.S.H. output are iodine deficiency (Axelrad and Leblond, 1955), goitrogens which inhibit thyroxine synthesis (Griesbach and Purves, 1945), partial thyroidectomy (Logothetopoulos and Doniach, 1955) and irradiation of the thyroid (Maloof *et al.*, 1952).

The sequence of events in the development of tumours is as follows: first, generalized hypertrophy and hyperplasia of the thyroid; second, the focal development of adenomata, sharply demarcated areas with a morphology distinguishable from that of the surrounding thyroid tissue; third, malignant change associated with a gross increase in the size of the gland, with permeation of extra-capsular veins and often with metastatic deposits in the lungs. Once an adenoma or carcinoma has developed, goitrogenic treatment is not always necessary for its perpetuation. Removal of the goitrogen (Bielschowsky, 1945) or depression of T.S.H. secretion by thyroxine administration (Purves and Griesbach, 1947) has not led to disappearance of the tumours in thyroids examined three to eight weeks later though follicular neoplasms develop flattened cells and show an accumulation of colloid. A more precise investigation of the survival time of induced adenomas after withdrawal of goitrogen remains to be done and also long-term observation of such rats to see if adenomas ever turn malignant in the absence of goitrogenic treatment.

Most observers agree that the majority of thyroid carcinomas in humans arise in adenomatous goitres (Rundle, 1951). Mortality statistics have shown that although thyroid

carcinoma is a very rare cause of death, the incidence is significantly higher in endemic goitre districts (Wynder, 1952). Since iodine deficiency is the accepted major factor in the causation of endemic goitre, the situation is comparable with that found in animal experiments. The role of T.S.H. is to some extent confirmed by the findings of hypertrophied follicular cells and diminished colloid in the thyroids of children and adolescents with endemic goitre. In the subsequent adenomatous goitres of adults, however, the non-neoplastic thyroid tissue is often rich in colloid and the cells are not obviously hypertrophied. Thus, one can only put forward the possibility that excessive T.S.H. stimulation in childhood and adolescence may leave a legacy of adenomas which show up in later life, after the stimulus to hypertrophy has ceased. Factors in the causation of the rare transformation of such adenomas into carcinomas are unknown and not obviously connected with T.S.H. stimulation.

With regard to radiation as a factor in the production of human thyroid carcinoma there have been recent reports from the U.S.A. which find in a proportion of cases of thyroid carcinoma in children, a history of X-irradiation to the thyroid in infancy in the treatment of an enlarged thymus or tuberculous lymph nodes of neck. The association appears clear. The incidence in one series (Simpson *et al.*, 1955) was 6 thyroid carcinomas in 1,400 patients who had had irradiation to the thymus.

The problem of goitrogens and irradiation of the adult thyroid is largely that of the treatment of thyrotoxicosis. Neither treatment has been followed by a crop of thyroid carcinomas. A comparison of rats with humans suggests that goitrogen treatment is not prolonged enough to be carcinogenic since carcinogenesis requires a maintained goitrogen administration for at least half the rat's lifetime. So far there have been descriptions of the late development of thyroid adenomas but not carcinomas following ^{131}I therapy of thyrotoxicosis (Lindsay *et al.*, 1955).

Carcinomas may arise in sporadic as well as endemic adenomatous goitres. But the ætiology of the sporadic goitres and the possible role of T.S.H. in their development have not been clarified. Nor is there any ætiology known of the rapidly-growing anaplastic carcinomas occasionally seen in the elderly patient with a previously normal thyroid.

Conclusion.—The results of animal experiments have confirmed the ætiological factor of goitre in the development of thyroid carcinomas and suggest that prolonged excessive T.S.H. secretion is carcinogenic to rats. Endemic goitre is almost certainly produced by an excessive secretion of T.S.H. due to iodine deficiency. But the role of T.S.H. in the induction of carcinomas in human adenomatous goitres is by no means settled. The human infant thyroid appears susceptible to the carcinogenic action of radiation. ^{131}I therapy of thyrotoxicosis has so far not proved carcinogenic. Small doses of thyroxine, sufficient to prevent excessive pituitary secretion of T.S.H., in the treatment of goitre, with or without surgery or radiotherapy, might prove beneficial in lowering the incidence of adenoma production and hence carcinoma.

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Mr. J. E. Piercy: Of the 1,700 thyroid operations performed at the New End Clinic in the past five years, 58 (or just over 3%), were for cancer of the thyroid. 7 of these were found in toxic goitres, 2 of them in primary toxic goitres. The remaining 51 cases were found in the non-toxic nodular goitre. In fact 8% of non-toxic nodular goitres operated on were malignant, the tendency to malignancy being particularly marked in the discrete adenomata. This high incidence probably depends in part on our being a goitre unit, for of the 58 neoplasms undergoing operations, 27, or nearly half, were referred from other hospitals.

Certain types of carcinoma of the thyroid give rise to more difficulty in pathological diagnosis than carcinoma of any other organ, and pathologists hold very divergent views on

the criteria of malignancy. Occasionally sections are examined by several pathologists all giving different opinions. Sometimes the problem is only solved by the appearance of a secondary deposit.

Our malignant tumours fall into three main categories:

(1) The majority arise in pre-existing benign adenomata. Histologically these vary from a well-differentiated carcinoma of low malignancy to a more rapidly growing partially-undifferentiated growth.

(2) The same may arise *de novo* in a lobe not the site or an adenoma.

(3) The undifferentiated carcinoma. This includes all other malignant growths—scirrhous, small and large cell and carcinomata displaying sarcomatous tendencies.

True reticulo-lympho-sarcomata grow rapidly and only temporarily respond to deep X-ray therapy. There is a definite percentage of tumours so undifferentiated that the type of malignancy cannot be determined.

Taking all differentiated carcinomas, the presence and amount of papillary tissue determine prognosis, the more papillary tissue found the slower growing and less malignant the tumour. The true papillary tumour is a slowly-growing neoplasm giving rise to a chain of large soft secondary nodes often as large as the thyroid lobe itself; whilst the primary carcinoma in the lobe may be too small to be detected by the naked eye. Our practice is to do a total thyroidectomy with the removal of involved glands.

The prognosis in carcinoma of the thyroid is in inverse proportion to the certainty of clinical diagnosis; those diagnosed in the Clinic with certainty having a hard, irregular and fixed mass, pressure symptoms and a husky voice. They have grown beyond the capsule of the thyroid and are often beyond the scope of complete surgical removal. Operation, however, is still undertaken. Another very important factor in prognosis is the speed of onset. Those occurring and increasing in size within a few weeks or months usually terminate fatally, particularly in the upper age group. Much in prognosis must depend on speed of onset, presence of pressure symptoms and the age of the patient. Unlike cancer elsewhere in the body, carcinoma thyroidea is more malignant in the aged than in the middle-aged and young.

Our cases ranged from the ages of 12 to several of 80. In the death-dealing upper age groups of 60's and over, we had 11 cases. All were clinically obvious, of which 9 had tracheotomies performed during the thyroidectomy, 7 dying within a few weeks to a few months of operation. They had been referred to the Clinic too late, even though they had had increasing pressure symptoms for months and goitre for years. The majority were undifferentiated carcinomas or reticulo-sarcomas. Very occasionally a pleomorphic giant-cell carcinoma or a reticulo-sarcoma may appear and advance so rapidly that no form of treatment can be given. It is of interest to note that in 3 cases of this upper age group, the carcinoma was found in a lymphadenoid or Hashimoto goitre; two were undifferentiated carcinomas and terminated fatally while the case of the differentiated papillary type is as expected, still alive and well. Perhaps all lymphadenoid goitres should be removed on this indication only without considering other forms of treatment.

The prognosis in the middle and younger age groups is infinitely better; the carcinoma more often being differentiated, containing papillary tissue and the majority commencing in a discrete adenoma. The lumps may have been present for months or even years but with a recent increase in size and change in consistency. Of the 5 who died in this group of 47 cases, all were approximately 50 years of age, 3 resembled the fatal elderly group in all respects—clinically obvious carcinomas, rapid onset, undifferentiated in type and early death. The remaining 2 cases, also clinically obvious, were differentiated carcinomas. They lived two and three years respectively, the first having been referred with a collapsed vertebra from a secondary thyroid carcinoma and dying from a squamous carcinoma of the bladder; the second finally succumbed from secondaries in the meninges. Both had undergone total thyroidectomy, radioactive iodine therapy and deep X-rays.

All of the 16 cases resulting in death were recognized as having obvious cancer of the thyroid at their first attendance at the Clinic. That is my main criticism, for the majority had had goitres for years and symptoms of pressure and pain and an increase in the goitre for several months, pointed to malignant changes. To recommend that the non-toxic nodular goitre does not require treatment until such symptoms appear often condemns such patients to a state where surgery can offer little help.

Of the 42 patients alive and well 7 were undifferentiated carcinomas; the diagnoses, however, and this is the important point, were made either during the operation or microscopically. The other 35 cases were differentiated carcinomas, 2 only being obvious on clinical examination, 19 at operation and 14 microscopically.

Those recognized either clinically or at operation underwent total or near total thyroidectomy; certainly the involved lobe should be entirely removed with the adherent strap

muscles and any enlarged nodes. Our procedure for the past few years has been total or near-total thyroidectomy.

Those cases showing microscopic evidence of malignancy would have had a wide excision of all nodular tissue or a near lobectomy in the case of a discrete adenoma. We have re-operated in certain selected cases and performed a total thyroidectomy to allow for radio-iodine therapy to secondary deposits in bones or lungs should they occur later.

I have mentioned the low-grade well-differentiated papillary carcinoma as having the best prognosis. Several cases have been referred from other hospitals, invaded lymphatic nodes having been removed followed by the appearance of yet other nodes. It is our practice in such cases to undertake a total thyroidectomy with removal of the involved glands which may often extend from the tip of the mastoid process to well under the clavicle. In most of these apparently normal thyroid lobes a small area of primary malignancy can be found.

The nodular goitre in children and young adults is to be looked upon with grave suspicion as it may well prove to be malignant or at any rate to recur after operation and after re-operation, the final recurrence being frankly malignant. We recommend that a recurrence within a few years of operation in these young people be treated either by a near-total thyroidectomy or by radioactive iodine ablation.

Carcinoma of the thyroid unlike carcinoma of most other organs can be notoriously difficult to recognize at the time of operation and may easily be confused with degenerative, cystic and fibrous processes. I must admit to have performed total thyroidectomy for a multiple myeloma of the skull, for eosinophil granuloma of the thyroid and for an osteogenic sarcoma of the femur with lumps in the neck. Other cases have proved to be invasion of the thyroid from carcinoma of the œsophagus, bronchus and post-cricoid regions. One case proved to be a widespread infiltrating Riedel's thyroiditis commencing in an aberrant thyroid nodule, the thyroid lobes themselves being normal.

We are tending more to perform total thyroidectomy, where possible, on all cases of clinically obvious carcinoma, unilateral or bilateral with or without secondaries, to allow for radioiodine therapy, should secondaries be present or arise later in other parts of the body. None of our total or near-total thyroidectomies have been followed by tetany or permanent voice changes; whilst the potential myxœdema is easily controlled, and without hardship to the patient, by means of thyroid or thyroxin by mouth.

All discrete adenomas are widely removed; if large, a near lobectomy is performed. If microscopy proves it to be malignant, further treatment depends on the type of malignancy and as to whether or not its capsule or blood vessels have been invaded. The decision should be observation only, in the low-grade type of neoplasm without secondaries and with an intact capsule and uninvolved vessels; whilst total thyroidectomy or radioiodine ablation of the thyroid remnants *should* be undertaken if the reverse is the case. Following operation 17 of our cases were given deep X-ray therapy and 34 were investigated by means of radioactive iodine of which 14 underwent radioiodine therapy.

The results of surgery in the hidden or obscure carcinoma are excellent, in the clinically suspect carcinoma good, but in the clinically obvious cases the results are bad.

These facts lead us to be still more dogmatic in regard to the removal of all discrete non-toxic adenomas and nodular goitres. If the recommendation is not possible to follow, because of long waiting-lists and scarcity of beds, at any rate, operation should be undertake at the first suspicion of malignancy when the results are still good and not left until the condition is obvious when results are bad.

Dr. E. E. Pochin:[1]

Radioiodine Treatment of Thyroid Carcinoma

During the last twelve years, in which many hundreds of patients with thyroid carcinoma have been receiving radioiodine treatment, certain factors have become clearly established about the selection of patients and the regime of dosage. It is now becoming possible also to describe the immediate response to radioiodine, although the ultimate prospects cannot yet be known, particularly since the differentiated thyroid carcinomas may progress very slowly even without treatment and since all forms of radiotherapy require long periods for proper assessment. This summary will therefore be based on the initial or continuing response of some 90 patients with thyroid carcinoma, proved histologically, for whom radio-iodine treatment has been attempted, in work done in conjunction with Dr. Gwen Hilton, Dr. K. E. Halnan and Dr. R. M. Cunningham; no case, however, having yet been followed for longer than six years.

The first factor influencing the selection of patients for this treatment is that radioiodine alone is never as reliable as total surgical excision of a thyroid carcinoma. The following

[1]Work undertaken on behalf of the Medical Research Council.

discussion is therefore of tumours which prove to be inoperable, total removal having been attempted whenever its success seemed at all likely.

The second factor, which is now becoming equally clear, is that anaplastic thyroid cancers rarely respond to radioiodine treatment whereas differentiated ones quite commonly do so. An initial biopsy is therefore most important, not only to confirm the diagnosis of a primary thyroid carcinoma, but because histological criteria are essential to distinguish the anaplastic tumours which are normally best treated by external radiotherapy, from the differentiated groups which if inoperable should, in our view, normally be treated by radioiodine. The distinction is not entirely clear cut, since anaplastic tumours do occasionally respond to radioiodine so that for a slowly-growing tumour of this type, for which other forms of therapy have failed, radioiodine may, perhaps, be worth trying. On the other hand, some locally recurrent papillary thyroid carcinoma may be effectively controlled by surgery alone for long periods. In general, however, radioiodine appears to be of value in the treatment of inoperable but differentiated carcinomas of the thyroid, whether with colloid-filled follicles or with a predominantly papillary pattern.

A third factor in this form of treatment is that such tumours will rarely concentrate radioiodine and prove amenable to treatment by this means while normal thyroid tissue remains in the body. Radioiodine uptake commonly develops only after ablation of the normal thyroid gland, and with, or soon after, the development of myxœdema. The necessary preliminary for radioiodine treatment, therefore, is ablation of the thyroid, either by a total thyroidectomy or by means of radioiodine.

The preparation for radioiodine treatment has, then, a number of surgical aspects:

(1) Biopsy is important, not only in diagnosis but in the selection of treatment according to tumour differentiation.
(2) Radical tumour excision should be attempted if it seems at all likely to be practicable.
(3) Total thyroidectomy may be needed before radioiodine treatment is started.
(4) The excision of any large tumour mass from the neck may improve considerably the prospects from radioiodine treatment even though moderate amounts of tumour tissue remain.
(5) It is often desirable to remove, if possible, any tumour mass which is threatening to cause tracheal obstruction, both because radioiodine may not become effective during the two or three months before myxœdema develops, and also because therapeutic doses may occasionally cause transitory tumour swelling or œdema.
(6) If the trachea cannot be freed, tracheotomy may become necessary.

The initial step in treatment, therefore, involves microscopic examination of the tumour, either by frozen section at the start of operation, or perhaps better, by a preliminary biopsy. If the tumour proves to be differentiated, and if a radical resection is impracticable, the aim of the operation should shift to an attempted total thyroidectomy with freeing of the trachea, if possible, and otherwise the removal only of such part of a large tumour mass as is easily resected, the remainder being left for treatment by radioiodine.

Often, however, after an initial biopsy, further operation will appear undesirable. This will be the case if the tumour is certainly inoperable and if a total thyroidectomy is likely to be awkward and incomplete owing to disturbance of neck structures by earlier operations, radiotherapy and the presence of active tumour tissue; and particularly if the tumour is not of large mass in the neck and is not immediately threatening the trachea. In these cases, thyroid function can equally well be abolished by an 80 millicurie ablation dose of radioiodine. For thyroid ablation, therefore, surgical treatment will gain time if a total thyroidectomy and substantial tumour resection can be expected, but will lose time if thyroid tissue remains and no considerable tumour resection is possible.

Full myxœdema usually develops at between two and three months after thyroid ablation, and the iodine uptake of the tumour commonly becomes maximal then or soon after. It appears quite common that thyroid tumours only develop uptake with the onset of myxœdema and it is uncertain whether any further stimulus is of value once myxœdema has developed, although treatment with thiouracil derivatives is often given at this stage in the hope of increasing the likelihood or efficiency of uptake.

When radioiodine uptake in tumour tissue is demonstrable, radioiodine treatment may be started, although various clinics differ widely as to the amount of such uptake they require before starting treatment. In our opinion the percentage of the dose concentrated in tumour tissue cannot rationally determine the giving or postponement of treatment when neither the mass nor the radiosensitivity of the tumour is known. We would start treatment if uptake was clearly detectable in tumour tissue by normal counting methods in a patient who had become myxœdematous; and would regard the response to such treatment as the best criterion as to its value.

Measurements of the percentage of the radioiodine dose concentrated at tumour sites can, however, be of great value in following the progress of treatment, and we normally give repeated 150 millicurie doses until this figure falls below 0·01 % or uptake is no longer

detectable, widening the interval between doses as the percentage falls (Pochin *et al.*, 1954). We use an interval of six to eight weeks at first and while the total uptake exceeds 1%, giving doses every three or four months when the figure has fallen to 0·1%, and continuing annual test doses when uptake is no longer detectable. From the time when myxœdema has developed and uptake is established, the patient receives thyroxine continuously except for the four weeks before each dose.

On such a regime, radiation injury to the bone marrow rarely causes difficulty except in patients with bone metastases. In these patients, radioiodine may cause initial and clinically valuable improvement and relief of symptoms, without evidence of marrow aplasia for many months. After perhaps a year, however, a progressive fall in red cells, white cells or platelets may occur, presumably because radioiodine is being concentrated in bone marrow by metastases diffusely involving the bones, and the radioiodine doses need to be diminished, spaced more widely or discontinued.

In patients without bony metastases, an iodine-concentrating thyroid carcinoma may often be treated with successive radioiodine doses until the tumour mass is no longer detectable either to palpation or radiologically, and its radioiodine uptake decreases correspondingly and ceases to be detectable. New metastases may appear during treatment and in turn respond to radioiodine, although in some cases they may progress in spite of further dosage.

In general, however, the majority of differentiated thyroid carcinomata appear to concentrate radioiodine after thyroid ablation, and to show a clinically useful response to treatment at least during the first few years, except in patients with bony metastases where the useful period of treatment is limited to about a year by the development of marrow aplasia.

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Mr. Selwyn Taylor said that with his registrar Mr. R. Alhadeff and a Research Fellow in Pathology from Canada, Dr. Foster Scott, he had attempted to correlate the clinical picture of the disease with its pathological type and they had been greatly assisted in this by Dr. I. Doniach. Excluding patients upon whom they did not have enough information, there were 67 from Hammersmith Hospital in the last seven years suitable for this review and he had added 6 others who have come under his immediate care elsewhere, making a total of 73.

They had used the classification of Warren and Meissner's with slight modifications, but it must be stressed that papillary areas were often seen in the follicular carcinomas and only those tumours which showed a predominantly papilliferous type had been placed in the previous group. In the United States he had found that the tendency was to put all tumours showing any papillary areas into this group and he believed that this explained the high incidence of papillary tumours reported there.

Taking the papillary group first, the patients were the youngest seen, none of the 14 had died, and in 1 the disease had apparently been present for twenty-three years. The treatment had been surgical and conservative, in keeping with the local spread by lymphatics, except for the invasive type where block dissection of the neck had been done on five occasions.

The follicular type were perhaps the most interesting, not only because of the wide variations in malignancy, but because they often retained some degree of thyroid function and so could be investigated and treated with radioactive iodine, as Dr. Pochin had so ably shown. They presented for treatment mainly in the 30–40 and 60–70 year age groups; of the 19 well-differentiated follicular ones, 8 were dead within five to six years of first coming under treatment; of the 12 less differentiated, 7 died in six to seven months of first being treated. Metastasis was commonest in bone and next in lung.

The anaplastic group, subdivided into large and small cell types, made the most dismal showing. Of the 7 giant cell tumours, the longest survival was five months; of the small cell ones, 17 in all, only 4 were still alive and all the others died within a year.

Only a careful appraisal of the histology of thyroid cancer would enable one to judge the probable course and prognosis of the disease, except for that small group of borderline cases where the dividing line between the hyperplasia of simple nodular goitre seemed to merge into the hyperplasia of malignancy. Indeed it was not impossible that the same mechanism, i.e. over-production of T.S.H. was the cause of both, as Dr. Doniach had said.

Mr. H. H. G. Eastcott asked Mr. Piercy from what number of cases of Hashimoto's disease the 3 cases of thyroid carcinoma were drawn. Hashimoto's disease, he said, was a common and rather harmless condition, and he felt that total thyroidectomy was too radical a method of treating it, on the slight chance that it might contain a carcinoma.

Mr. E. G. Slesinger drew attention to an unusual type of carcinoma occurring in young children of which he had seen two examples. In these cases there was a goitre, which on biopsy proved to be a carcinoma, associated with multiple secondary deposits in the lungs, giving a "snow-storm" appearance. In spite of this children remain well, in his cases one for over seven years and the other for four years to his knowledge and as far as he knew were still well. In some cases the lung deposits appear to regress on thyroid medication, while in others there is no effect.

He was not aware of any previous description of this peculiar type of case.

Section of Orthopædics

President—Sir REGINALD WATSON-JONES, M.Ch.Orth., F.R.C.S.

[*October* 4, 1955]

Myositis Ossificans Progressiva.—H. D. W. POWELL, F.R.C.S. (for R. C. F. CATTERALL, M.Chir., F.R.C.S.).

D.I., female, aged 4.

History.—First seen in the Physical Medicine Department when ten months old with left-sided torticollis; this was easily correctible by stretching but owing to non-attendance, treatment did not commence until she was 18 months old. At the age of 2¼ she was referred to the Orthopædic Department. X-rays of cervical spine, some under anæsthesia, showed no detectable abnormality. Bilateral hallux valgus and short great toes were noticed at this time, as also were the peculiar bony changes at the lower ends of both forearm bones. Treatment with a plastic neck collar followed by neck tractions produced no improvement.

In May 1955, aged 4, cervical spine X-rays showed fusion of the lateral masses in the lateral views, i.e. posterior ankylosis of the cervical spine (Fig. 1). X-rays of the whole skeleton were then taken:

The lower ends of both forearm bones on each side show outgrowth (Fig. 2); identical

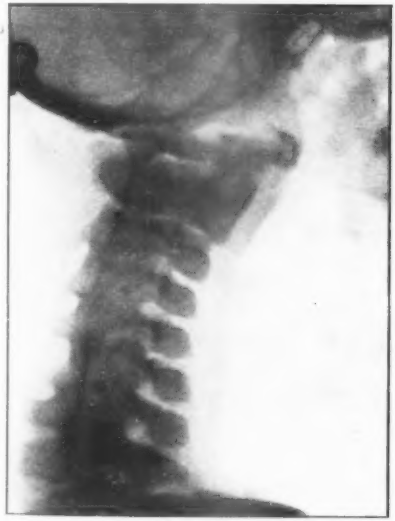

FIG. 1.

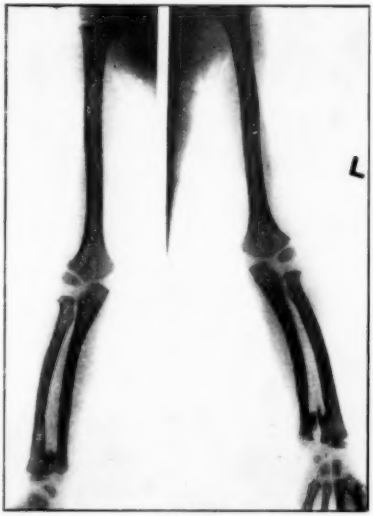

FIG. 2.

appearances can be seen in Hunterian skeleton in the museum at the Royal College of Surgeons.

The hands show very short first metacarpals (Fig. 3).

There are curious thickenings on the under surface of both femoral necks and hyperostosis on the upper and outer aspects of each femoral cortex (Fig. 4).

Both feet show hallux valgus deformities combined with large misshapen first metatarsals and there is only one phalanx in each great toe (Fig. 5).

Clinical photographs (Fig. 6) show the position of the child's neck, the short thumbs and great toe deformities.

On examination.—Under general anæsthesia there is only a little forward flexion and a little lateral flexion in the cervical spine. There is also considerable limitation of pronation and supination in each forearm.

There has as yet been no evidence of any temporary localized swellings in head, neck, trunk or elsewhere.

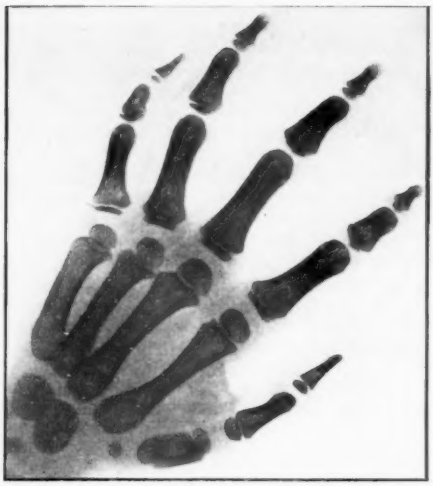

FIG. 3.

FIG. 4.

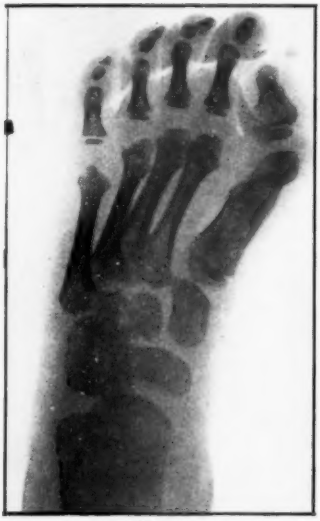

FIG. 5.

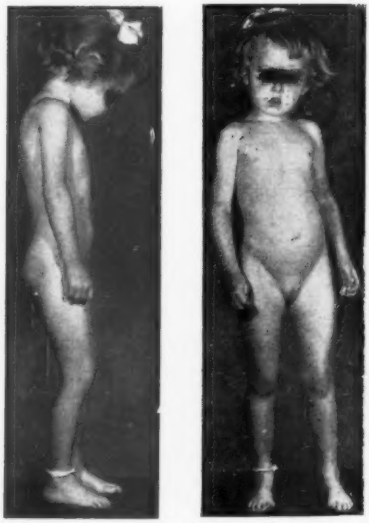

FIG. 6.

Investigations.—Blood examinations, including serum alkaline phosphatase, have been within normal limits.

Treatment.—Out-patient physiotherapy has been abandoned as producing no benefit. Cortisone has been considered but has not yet been used.

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The discussion was concerned with the indications for the use of cortisone in this case. It was ultimately agreed that it should be reserved for any flare-up as shown by increase of pain or stiffness.

Spastic Pes Varus.—ROY H. MAUDSLEY, F.R.C.S.

D. F., female, aged 10, first complained of pain in the right foot eight months previously. The onset was gradual and there was no history of trauma. The pain was worse on walking and was relieved by rest.

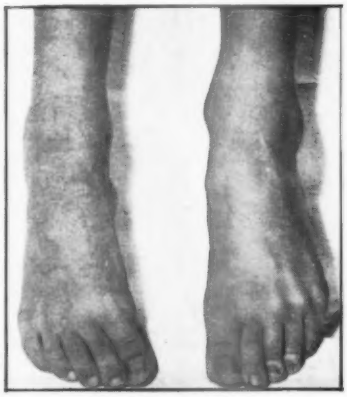

FIG. 1.

On examination.—She appeared a healthy girl. The right foot is held in a moderate degree of varus (Fig. 1). There is spasm of the tibialis anterior and eversion is resisted. She walks on the outer border of the right foot. The left foot is normal in appearance though eversion and inversion are slightly restricted.

Radiographs (1955) reveal well-marked bilateral calcaneo-navicular articulations (Fig. 2*a*, *b*). Radiographs of the right foot taken in 1953 for minor trauma revealed no abnormality (Fig. 3*a*, *b*).

Investigations.—Blood count and E.S.R. were within normal limits.

Treatment has been conservative. Examination under general anæsthesia permitted the foot to be brought to the neutral position and a walking plaster was applied and maintained for three months. The pain was relieved by this, but recurred after removal of the plaster. Physiotherapy did not help.

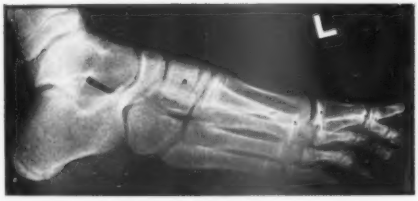

FIG. 2A.

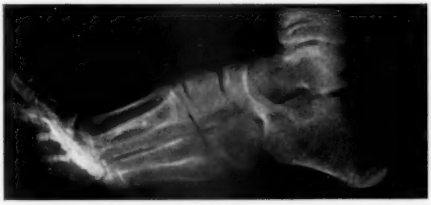

FIG. 2B.

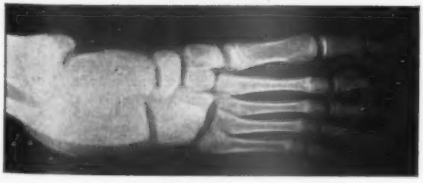

FIG. 3A.

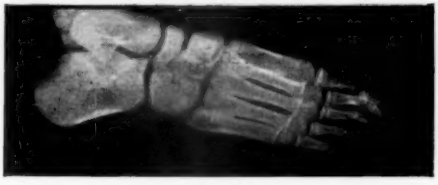

FIG. 3B.

No similar case had been found in the literature. The name of spastic pes varus was suggested as it appeared to parallel the condition of spastic pes valgus.

The discussion was concerned with the role of the bony bridges in causing spasm. It was ultimately agreed that the bridge was a cause of rigidity rather than spasticity, which latter was traumatic in origin.

In this particular case there was unanimous agreement that no active treatment should be undertaken until the child was 12 and then a triple arthrodesis should be contemplated if her symptoms warranted any surgical treatment.

Paralytic Flat Foot Treated by Triple Tendon Transplantation.—A. C. BINGOLD, F.R.C.S.

L. H., female, aged 7. Poliomyelitis at age 2 left her with a flat left foot caused by complete paralysis of the left tibialis anterior and posterior (Figs. 1 and 2).

At age 6 a triple tendon transplantation was performed (Fig. 3).

(1) The heel cord was stitched to the inner side of the calcaneum.

(2) The tibialis posterior tendon was divided 2 in. above the medial malleolus. The distal end was stitched to the extensor hallucis longus tendon in front of the ankle.

(3) The peroneus brevis tendon was stitched to the tibialis posterior tendon near its insertion.

The foot was protected by a plaster cast for five months. Shape and function nineteen months after the operation were satisfactory (Figs. 4 and 5).

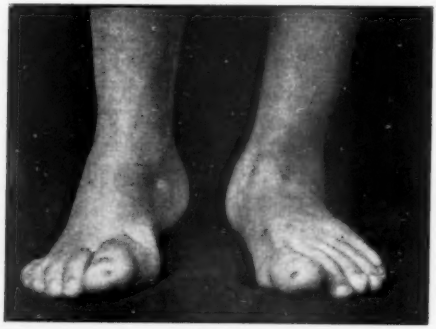

FIG. 1.

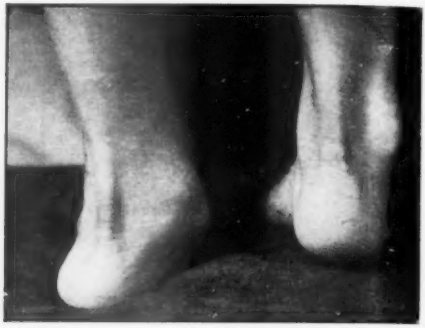

FIG. 2.

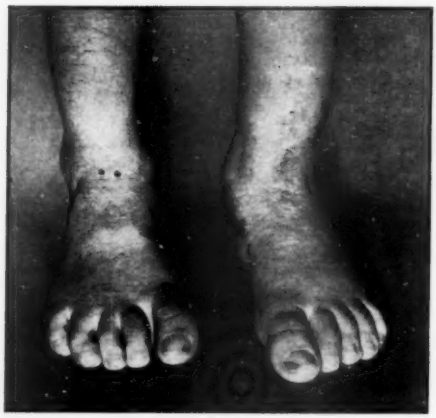

FIG. 4.

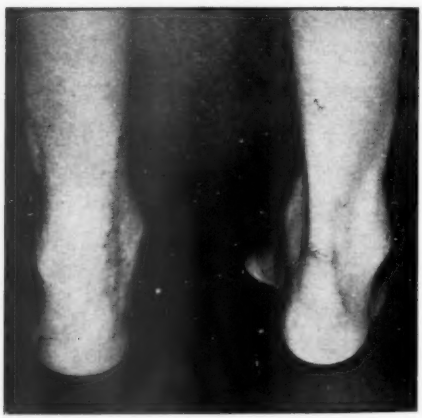

FIG. 5.

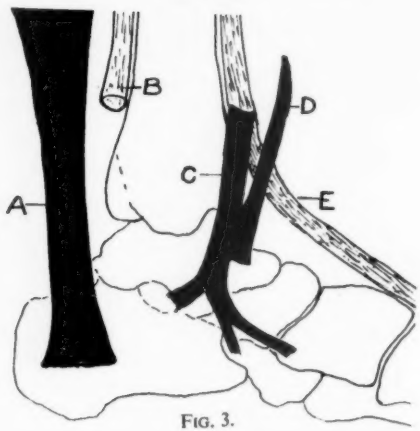

FIG. 3.

FIGS. 1 and 2.—Feet before operation.

FIG. 3.—Principle. A=heel cord. B=proximal end of tibialis posterior. C=distal end of tibialis posterior. D=peroneus brevis. E=Extensor hallucis longus.

FIGS. 4 and 5.—Feet nineteen months after the operation.

Additional experience with this new method is necessary, but even if the present good correction is lost or a new deformity develops the child can be treated by external splintage followed by a triple arthrodesis at the age of 12. It is intended to show her again in five years' time.

An Unusually Large Foreign Body in the Hand.—F. G. St. Clair Strange, F.R.C.S.

A farm labourer had his right hand impaled by a Rototiller blade, and was brought to hospital with the foreign body *in situ*. [The blade (Fig. 1), which measured $4\frac{7}{8}$ in. by 5 in. overall and weighed $9\frac{3}{4}$ oz. had entered the ulnar border of the wrist and emerged through the palmar aspect of the thumb. Owing to its curvature, removal was impossible without open operation, when it was found to be lying between the tendons and nerves in front of the wrist and within the abductor pollicis brevis.]

Fig. 1.—The rototiller blade, measuring $4\frac{7}{8}$ in. × 5 in. The width of the blade is up to $\frac{7}{8}$ in. and its thickness $\frac{1}{4}$ in. $\frac{1}{4}$

Post-operatively, there was temporary median palsy and anæsthesia, but this recovered, and he was left with an almost normally functioning hand, the only residual disability being incomplete flexion of 5th finger.

A general discussion on the case showed that the majority of members were in favour of postponing any attempt to free the flexor tendons to this finger, as further improvement by resolution was to be anticipated.

Progressive Familial Hypertrophic Polyneuritis (Dejerine-Sottas Syndrome, 1893).—Michael J. Cox, M.B.

Miss B. W., aged 55.

She was born with normal feet except for a high instep but she always had a deformed back.

Aged 7 her family noticed she would trip over easily and she began to turn her feet inwards and then between the ages of 11 and 14 she had special exercises for her feet.

Aged 14 she underwent an operation for bilateral pes cavus. She then walked fairly well until the age of 30 when "a sudden shock took her off her feet". Since then she has crawled most of the time on her knees, occasionally pulling herself up to stand on the dorsum of her feet.

Aged 45 onwards she began to develop ulcers on both feet which have become very painful in the last few months.

Her right hand is deformed but has a good grip while there is good function in the left hand.

Social history.—She has been caring for her mother for many years doing quite a lot of housework but no cooking. She has not been in a shop for about twenty years and she has not been out of the house for five years.

Family history.—Her grandfather suffered from "curvature of the spine" and was called "high-kicker" because of an abnormality of his feet. Her father suffered from a minor abnormality of his feet; one of her aunts had talipes equino-varus and absent deep reflexes, while another aunt suffered from curvature of the spine. One of her cousins suffered from "club feet" and two other cousins suffered from the fully-developed syndrome similar to this patient. Two of her nieces suffered with "curvature of spine", one associated with pes cavus, and one has absent deep reflexes.

This family has been previously reported by Russell and Garland (1930).

Physical examination.—Cranial nerves normal. Gross kyphoscoliosis convex to right in the thoracic region and to the left in the lumbar region.

Upper limbs: There was wasting of the arms and severe wasting of the intrinsic muscles of the hand, right worse than left. There were flexion contractures at the proximal interphalangeal joints of all fingers of the right hand and of the ring and little fingers of the left hand. Ulnar nerves thickened, right larger than left. Reflexes absent. No sensory disturbance.

Abdominal reflexes absent.

Lower limbs: wasting of thighs and calves. Thickened callosities over both tibial tubercles and thickened infrapatellar bursæ. Power good in both hips and knees. Both lateral popliteal nerves were greatly thickened.

Feet (Figs. 1 and 2): Gross bilateral talipes equino-varus, A large penetrating ulcer under the right heel and a smaller one on the left. The reflexes were absent but there was no sensory disturbance.

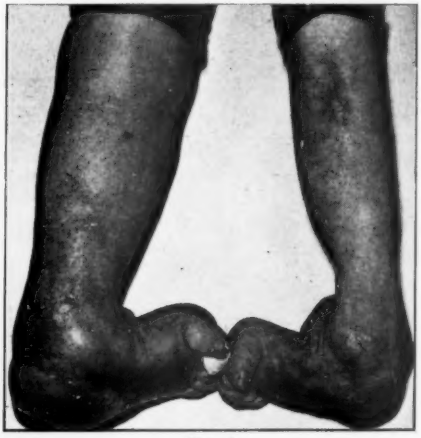

FIG. 1.

FIG. 2.

Progress.—The ulcers were cleared up with local treatment and systemic chemotherapy. Then a left Syme's amputation was performed by Mr. H. Osmond-Clarke. The os calcis was found to be very mushy and was removed piecemeal. A right Syme's amputation was performed on 15.10.55.

Pathology.—Macroscopic: Dissection of the amputated left foot showed extensive fatty replacement of the flexor digitorum brevis and other muscles. The cartilage of the talus was greatly eroded by osteoarthritis. The nerves were diffusely thickened (medial plantar, 0·5 cm. in diameter; lateral plantar 0·35 cm. in diameter at points close to their origins). There was less thickening of the anterior tibial, musculo-cutaneous and sural nerves.

Microscopic: (1) *Nerves.* The five nerves mentioned were examined in longitudinal and transverse sections. The thickening is mainly due to a great increase of collagen throughout the epi-, peri- and endo-neurium. In the first two layers it is dense and hyaline; in the last mentioned, fibrillar. There is also proliferation of the endoneurial cells and, occasionally, of similar cells in the perineurium. In the endoneurium the cells tend to form onion-like whorls; the individual cells are separated by delicate collagen fibres. These whorls are formed about axis-cylinders, but a large proportion of the latter have undergone destruction. There is no inflammatory cellular reaction other than a rare and small group of small lymphocytes. The blood vessels are not significantly altered.

(2) *Muscles.* In these there is gross replacement by adipose tissue. Such muscles as persist are almost all greatly atrophied, though a few are hypertrophic. There is conspicuous collagenous thickening of the endomysium. Attempts to demonstrate motor nerve-endings by the methylene-blue technique were unsuccessful.

Discussion.—This case is presented to show another of the indications for the Syme's amputation. By means of this treatment it is hoped to be able to mobilize this woman who has led such an incapacitated life for years.

This disease bears close resemblance to Charcot-Marie-Tooth peroneal atrophy while the enlargement of the nerves is seen in Von Recklinghausen's disease.

The possibilities are discussed by Russell and Garland (1930) who thought it advisable to class it as a separate entity.

Summary.—A case of familial hypertrophic polyneuritis, treated by Syme's amputation, is presented.

I should like to express my thanks to Sir Reginald Watson-Jones for his encouragement in the presentation of these two cases and to Professor Dorothy Russell for her very great help in preparing the report of the pathology of this case.

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[*This Meeting will be continued*]

Section of Pathology

President—Professor L. P. GARROD, M.D., F.R.C.P.

[*November* 15, 1955]

SYMPOSIUM ON LABORATORY ASPECTS OF BLOOD COAGULATION

INTRODUCTION

Dr. J. V. Dacie:

OUR knowledge of the mechanism of blood coagulation in man, and its disorders, has made astonishing progress in the last two decades. This brief introduction is an attempt to summarize our present knowledge of the coagulation factors and of the tests which may be used in assessing their activity.

Up to the beginning of the Second World War the laboratory investigation of patients suspected of suffering from a hæmorrhagic disorder almost certainly consisted of only two or at the most three tests: the measurement of the whole-blood coagulation time, the bleeding time and, perhaps, an estimation of the level of plasma fibrinogen.

An outstanding event was the introduction of methods for measuring prothrombin by Quick in 1935, and by Warner *et al.* in 1936. These techniques, which record the speed at which plasma is clotted by tissue (i.e. brain) thromboplastin, initiated an additional method of investigation which has proved extremely valuable, even if the tests, as at first introduced, do not in fact give a reliable measure of prothrombin.

Quick in 1943 made another important contribution, for he discovered that "prothrombin" consisted of two components, one of which was labile and not adsorbed by aluminium hydroxide. Quick's labile component of "prothrombin" was described independently and more fully by Owren, in Norway, who in 1947 called it Factor V (i.e., the fifth clotting factor—the other four factors being the blood platelets, prothrombin, fibrinogen and calcium). Factor V was originally thought to act as an accelerator of the conversion of prothrombin to thrombin.

Now I have to mention Factor VII (Factor VI, originally proposed by Owren as a derivative of Factor V, has faded into the background—it probably does not exist as a distinct entity). Factor VII is the name given in 1951 by Koller and co-workers in Switzerland to a stable substance present in plasma and serum which also was thought to have the property of accelerating the conversion of prothrombin to thrombin; its presence is required before brain thromboplastin can react with prothrombin and calcium, as in the ordinary Quick prothrombin-time test. Deficiency of Factor VII is in fact the main cause of lengthened prothrombin times in patients treated with dicoumarol, Tromexan or allied anticoagulants.

Factors V and VII are probably quite distinct; they have contrasting properties, for instance, in respect of stability (Factor V being labile, Factor VII stable) and ease of adsorption to aluminium hydroxide or barium sulphate, and they probably act at different stages in coagulation and in a different way.

Now I must mention two other factors—(i) antihæmophilic globulin (AHG) and (ii) the Christmas factor. (i) Well before Factors V and VII were discovered it began to be realized that normal platelet-free plasma contains a substance which in small proportion could accelerate to a marked degree, and even bring to normal, the clotting time of a hæmophiliac. This had been observed as long ago as 1911 by Addis but, unfortunately, he failed to appreciate the significance of the observation. Quick in 1947 introduced the term "thromboplastinogen" to describe this plasma factor. At the present time the material is usually referred to as antihæmophilic globulin (AHG). There is abundant evidence that this substance is something distinct from Factors V and VII, and unconnected with the blood platelets.

(ii) The Christmas factor was named after a boy called Christmas who was a supposed case of hæmophilia (Biggs *et al.*, 1952). It was found, however, that, although he had a hæmophilia-like disease, his plasma, when added to hæmophilic plasma *in vitro*, restored the clotting time of the hæmophilic plasma to normal. His plasma contained, in fact, a normal amount of AHG, but lacked a hitherto-unsuspected clotting factor. The Christmas factor or plasma thromboplastin component (PTC) as it is known in America (Aggeler *et al.*, 1952) also appears to be quite distinct from antihæmophilic globulin or Factors V and VII. It is now known that about 15% of so-called hæmophiliacs lack the Christmas factor, i.e., they have Christmas disease (PTC deficiency or hæmophilia B).

The role of these newly-recognized factors in coagulation is, according to Macfarlane and Biggs (1955), as shown in Table I.

TABLE I.—THE POSSIBLE ORDER OF INTERACTION OF THE FACTORS CONCERNED IN BLOOD COAGULATION (after Macfarlane and Biggs, 1955).

Stage 1.—Antihæmophilic globulin + platelets —(Christmas factor)→ intermediate product.

Stage 2.—Intermediate product + Factor V —(Factor VII)→ thromboplastin.

Stage 3.—Prothrombin —(thromboplastin)→ thrombin.

Stage 4.—Fibrinogen —(thrombin)→ fibrin.

Stage 1 is initiated by contact of the blood with a water-wettable surface. Calcium is also required for the reactions to proceed.

Next, I must refer to two laboratory techniques. (i) The prothrombin-consumption test. By this test one measures the amount of prothrombin *not* utilized after blood has been allowed to clot. Normally, of course, practically all the prothrombin is consumed when blood clots; in hæmophilia, on the other hand, consumption may be grossly impaired, so much so that a hæmophiliac's serum may appear to contain more prothrombin than did his plasma. The prothrombin-consumption test suffers, as does of course the whole-blood clotting time itself, from being non-specific in that any disorder of coagulation, and also deficiency or inadequate functioning of platelets, leads to an impaired consumption of prothrombin. It is, therefore, of little or no use diagnostically.

(ii) The second test, the thromboplastin-generation test, is, however, of real practical value in differentiating the disorders of coagulation which are now recognized (Biggs and Douglas, 1953). In this test, the presence and activity of antihæmophilic globulin, Christmas factor and platelets can be tested for separately. The necessary reagents are shown in Table II. Sub-samples of the incubation mixture of (*a*) $Al(OH)_3$-treated plasma, (*b*) serum, (*c*) platelets and (*d*) calcium are added at one-minute intervals, with additional calcium, to normal citrated plasma. The clotting times of the citrated plasma substrate is a measure of the amount of active thromboplastin present in the mixture at the time of subsampling. Some results of actual experiments are shown in Table III.

TABLE II.—REAGENTS IN THE THROMBOPLASTIN-GENERATION TEST

Aluminium-hydroxide-adsorbed plasma (Used 1 in 5)
Supplies: Factor V
Antihæmophilic globulin

Serum (Used 1 in 10)
Supplies: Factor VII
Christmas factor

Platelet suspension

0·025 M *Calcium chloride*

Mixed together at 37° C. in equal volumes, the above reagents form the "Incubation Mixture". 0·1-ml. subsamples are taken at one-minute intervals and added (with an equal volume of 0·025 M calcium chloride) to 0·1-ml. volumes of citrated normal plasma. The clotting times of the substrate plasma are recorded.

TABLE III.—RESULTS OF THE THROMBOPLASTIN-GENERATION TEST IN HEALTH, IN HÆMOPHILIA AND IN CHRISTMAS DISEASE

Condition	Platelets used	Aluminium-hydroxide-treated plasma used	Serum used	Clotting times in seconds after incubation for: 1	2	3	4	5	6 minutes
Normal	normal	normal plasma	normal serum	26	10	9	9	11	—
Hæmophilia	normal	patient's ,,	normal ,,	40	40	34	32	32	35
	normal	normal ,,	patient's ,,	14	12	10	9	9	9
Christmas disease	normal	normal ,,	patient's ,,	36	29	25	29	26	26
	normal	patient's ,,	normal ,,	36	13	10	10	10	9½

Although there appear to be a whole series of clotting factors only prothrombin has been prepared in anything like a purified state. Factors V and VII, antihæmophilic globulin and Christmas factor are all as yet hypothetical substances. However, doubt as to whether

they are all separate entities, or whether some are related one to the other, should not be allowed to obscure the fact that they play a very important role in blood coagulation and in the pathogenesis of hæmorrhagic disorders in man.

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Dr. W. R. Pitney (Department of Pathology, Post-graduate Medical School of London)

The Laboratory Diagnosis of Hæmophilia

Since the introduction of the thromboplastin-generation test in 1953, we have examined in our laboratory 60 patients who are suffering from true hæmophilia (AHG deficiency) uncomplicated by other hæmostatic defects. Detailed coagulation studies were performed on these patients to obtain information concerning the relative sensitivities of the various tests of clotting function. Recently, a plasma AHG assay method based on the thromboplastin-generation test has been in use, and in 36 patients the degree of AHG deficiency, as determined by this method, has been correlated with the results of the coagulation times and prothrombin-consumption tests.

It was found both clinically and on the results of the coagulation tests that patients with hæmophilia could be divided into a moderately or severely affected group in whom diagnosis was usually straightforward, and a mildly-affected group in whom the more usual tests of clotting function were frequently normal. It is the purpose of this paper to summarize the experiences gained in the diagnosis of these patients, and to present a method of laboratory approach when confronted with a patient who may have hæmophilia.

43 patients suffered from moderate or severe hæmophilia. The diagnostic triad of sex-linked inheritance, a history of abnormal bleeding since early childhood, and a prolonged whole-blood coagulation time was commonly observed in this group. In 69% a positive history of abnormal bleeding in near relatives was obtained; all the patients were incapacitated to some degree by their disease; all showed a prolonged whole-blood coagulation time.

17 patients were suffering from clinically mild hæmophilia. The majority of these patients lead nearly normal lives. They comprised an older age group than the severely affected patients; 10 were over 21 years before the diagnosis was made. Several have successfully performed a period of military service with little or no trouble. Excessive bleeding following tooth extraction has been the major presenting problem. None of these patients has suffered from hæmarthroses. In 16, the whole-blood coagulation time was normal. In 8 (47%) there was a positive family history of excessive bleeding.

Diagnosis of Moderate or Severe Hæmophilia

Diagnosis was usually straightforward in these patients. Tests for capillary resistance, the bleeding time, Quick prothrombin-time test, platelet count, platelet morphology and plasma fibrinogen concentrations were normal. The prothrombin-consumption and thrombin-generation tests were abnormal, indicating deficient production of plasma thromboplastin during *in vitro* coagulation. Distinction from other thromboplastin-deficiency states, notably Christmas disease, could be made on the results of mixing tests or by the thromboplastin-generation test.

The Use of Mixing Tests in Diagnosis

When the plasma recalcification time was prolonged the corrective effect of preparations containing antihæmophilic globulin (AHG) could be tested *in vitro*. Normal plasma adsorbed with aluminium hydroxide ($Al(OH)_3$–treated plasma) and the reconstituted fibrinogen fraction of normal plasma both contain AHG but not Christmas factor. The addition of an equal volume of a 1 in 10 dilution of either preparation to AHG-deficient plasma will appreciably shorten its prolonged recalcification time. These preparations will not correct the defect in Christmas disease plasma. Normal serum contains Christmas factor but not AHG. Therefore, the addition of a one-tenth part of serum will correct the

prolonged recalcification time of plasma deficient in Christmas factor, but not of plasma deficient in AHG. Plasma from a patient with Christmas disease contains normal amounts of AHG and will correct the recalcification time of hæmophilic plasma as well as will normal plasma.

Tests based on the above principles are satisfactory only if the recalcification time of the test plasma is clearly prolonged. The formation of fibrin clots is often difficult to time accurately, and a disadvantage of such tests is that the recalcification time of the patient's plasma will often shorten spontaneously on standing. Therefore, tests must be performed soon after the plasma is collected. Nevertheless, mixing tests were usually quite satisfactory to establish the diagnosis in moderate or severe hæmophilia.

The Thromboplastin-Generation Test

The distinction between hæmophilia and Christmas disease was best made by the thromboplastin-generation test (*see* Introduction), even in severe cases. If warranted, mixing tests could also be performed, using thromboplastin-generation rather than plasma-recalcification times as the index of correction.

Tests for Circulating Anticoagulants

The development of a circulating anticoagulant is a rare complication in hæmophilia, and its exclusion is a necessary step in the complete diagnosis of patients with prolonged whole-blood coagulation times. The detection of anticoagulants is discussed by Dr. Hardisty.

Diagnosis of Mild Hæmophilia

Some mildly-affected hæmophiliacs only have symptoms when the hæmostatic mechanism is put under stress, as after tooth extraction or following surgical operations. Diagnosis of mild hæmophilia may be difficult, even with the use of sensitive techniques. The usual laboratory tests may give normal results and the thromboplastin-generation test is essential for diagnosis.

Relevant laboratory findings in a representative selection of these patients are shown in Table I. The prothrombin-consumption index (PCI) was determined by the method of

TABLE I.—LABORATORY FINDINGS IN SOME PATIENTS WITH MILD HÆMOPHILIA

Patient	Coag. time (normal 5–11 min.)	PCI (Normal 0–40%)	Thrombin-generation test	Thromboplastin-generation test
Co.	9½	34	N	N (8½/8 sec.)
Hu.	9	37	N	N (10½/9 sec.)
Da.	8	33	N	Ab.
Ta.	10½	25	N	Ab.
Br.	7½	49	N	Ab.
Sh.	9	60	N	Ab.
Er.	9	38	Ab.	Ab.
Ta.	11	7	Ab.	Ab.
Be.	8	95	Ab.	Ab.

Merskey (1950). The thrombin-generation test (Pitney and Dacie, 1953) was performed by recalcifying the patient's platelet-rich plasma and studying the evolution of thrombin by serially subsampling from the incubation mixture into tubes containing fibrinogen. The speed with which the fibrinogen clots is inversely proportional to the amount of thrombin present in the subsample.

In patients Co. and Hu., coagulation time, prothrombin-consumption index, thrombin-generation test and thromboplastin-generation test, as usually carried out, were normal. In the latter test, minimum substrate plasma clotting times of 8½ and 10½ seconds were obtained compared to normal values of 8 and 9 seconds, respectively. In these 2 patients, a modification of the thromboplastin-generation test using a higher dilution of the normal and test $Al(OH)_3$-treated plasma showed up a deficiency of AHG; this will be discussed later.

The remainder of these patients all showed an abnormal thromboplastin-generation test. In all except one, the whole-blood coagulation time was normal. The results of the prothrombin consumption and thrombin-generation tests were variable. Sometimes both tests gave a normal result; in other patients, one test was normal and the other abnormal. In the group of 17 patients, 12 showed a normal result with the prothrombin-consumption test. The thrombin-generation test was performed on the plasma of 12 patients. In 9, the result was normal.

It is clear that the whole-blood coagulation time is the least sensitive and thromboplastin-generation the most sensitive test for the diagnosis of mild hæmophilia. Prothrombin-consumption and thrombin-generation tests are intermediate between these others and of about the same order of sensitivity.

In patients in whom the results of the thromboplastin-generation test are equivocal, the use of higher dilutions of normal and patient's $Al(OH)_3$-treated plasma in the test may give clear evidence of AHG deficiency. The results of further testing of patient Co. (Table I) are shown in Table II. The patient's plasma diluted 1 in 5 reacted normally in the thrombo-

TABLE II.—THROMBOPLASTIN-GENERATION TESTS IN MILD HÆMOPHILIA
(Normal serum diluted 1 in 10 and patient's platelet suspension used throughout)

	Clotting times in seconds after incubation for:					
	1	2	3	4	5	6 minutes
Normal plasma 1/5	23	10	8	9	10	—
Patient's plasma 1/5	35	16	9	8½	9	—
Normal plasma 1/20 with added Factor V ..	60	30	12	10	9	9
Patient's plasma 1/20 with added Factor V	60	33	21	16	14½	14

plastin-generation test. Further dilution to 1 in 20 did not greatly affect the amount of thromboplastin produced when the normal plasma was tested, but an abnormal result was now obtained with the test plasma.

Since $Al(OH)_3$-treated plasma provides Factor V as well as AHG in the reaction, it is necessary to provide additional Factor V when testing in these higher dilutions. A convenient source of Factor V (without AHG) is provided by $Al(OH)_3$-treated plasma from a patient with *severe* hæmophilia. Such plasma contains practically no AHG. Stored whole at −20° C., hæmophilic plasma retains its Factor V activity for at least several weeks. The plasma, freshly adsorbed with $Al(OH)_3$, is added at a dilution of 1 in 5 to the other reagents when performing the thromboplastin-generation test at high plasma dilutions. Veronal buffer (pH 7·3) is preferable to saline for use as a diluent, although not essential.

AHG Assay

A method based on the thromboplastin-generation test has been devised for assaying the amount of AHG present in samples of normal and hæmophilic plasma (Pitney, 1956). The principle of the method consists in comparing the amounts of thromboplastin generated by various dilutions of a standard normal and of the test plasma when factors, other than AHG, necessary for the generation of thromboplastin are supplied in optimal amounts. The standard normal plasma is considered to contain 100% AHG. Using this method the range of plasma AHG concentrations in a group of normal people has been from 50 to 220%. In 36 patients with hæmophilia values from 0 to 25% have been obtained.

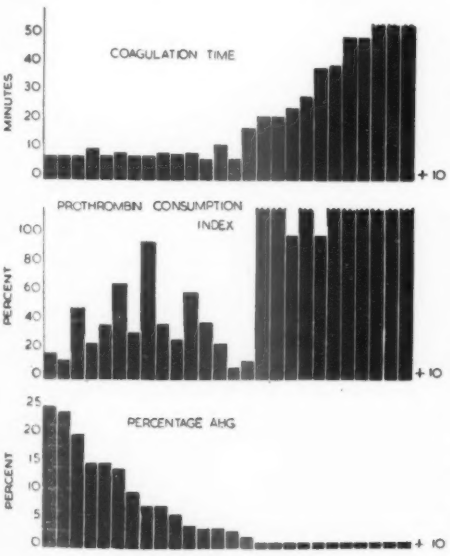

FIG. 1.—Whole-blood coagulation times, prothrombin-consumption indices and plasma AHG concentrations in 36 patients with hæmophilia. 26 patients are graphically represented. The other 10 showed similar results to the severe hæmophiliacs on the right of the figure.

In Fig. 1 the 36 patients have been graded according to the plasma AHG concentration. In this figure, the whole-blood coagulation time and the prothrombin-consumption indices have also been plotted. 15 patients suffered from mild hæmophilia. Their AHG concentrations ranged from 2 to 25%. The patient with a plasma AHG concentration of 2% had a coagulation time of 18 minutes; the coagulation times of the remainder were normal (11 minutes or less). The results of the prothrombin-consumption test were variable, but frequently normal. 21 patients with moderate or severe hæmophilia had plasma AHG concentrations between 0 and 1%; the whole-blood coagulation times and prothrombin-consumption indices were abnormal in all 21 patients.

Fig. 1 illustrates the insensitivity of the coagulation time as a diagnostic test in mild hæmophilia, for with plasma AHG concentrations above 2% the test is likely to be normal.

From observations on these patients, the following laboratory approach is suggested in the diagnosis of hæmophilia. If the patient has a prolonged coagulation time, the most likely diagnosis is a thromboplastin-deficiency state, probably hæmophilia. Disorders of the "prothrombin complex" (notably deficiencies of Factor V and Factor VII) may result in a prolonged coagulation time, but these can be excluded if the Quick one-stage test is normal. Gross fibrinogen deficiency is unlikely if a firm clot appears in the Quick one-stage test. An abnormal prothrombin-consumption test confirms the diagnosis of a deficiency of plasma thromboplastin. Distinction between hæmophilia and Christmas disease can usually be made on the basis of mixing tests. The thromboplastin-generation test is not essential for diagnosis in severe hæmophilia, although this test, if available, is to be preferred to mixing tests. The final step in diagnosis is the exclusion of a circulating anticoagulant.

In mild hæmophiliacs, mixing tests are of no value as the plasma recalcification time may not be prolonged. If the patient has a normal coagulation time, the thromboplastin-generation test must be performed before a bleeding disorder can be excluded. However, in such cases it is not necessary to perform tests for circulating anticoagulants.

Occasionally, the thromboplastin-generation test as usually performed may fail to reveal a very mild case of hæmophilia. In such an instance modification of the test using higher plasma dilutions should give an abnormal finding.

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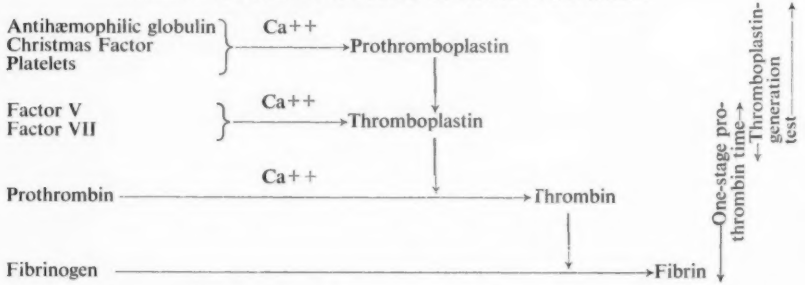
Dr. R. M. Hardisty (Louis Jenner Laboratory, St. Thomas's Hospital, London):

The Diagnosis of Some Other Coagulation Disorders

A hypothetical four-stage scheme of the blood-coagulation mechanism is shown in Table I. This scheme is largely based on results obtained by the use of the one-stage prothrombin time and the thromboplastin-generation test, and Table I also shows how these tests may be

TABLE I.—A SCHEME OF THE BLOOD-COAGULATION MECHANISM



used in conjunction to determine which stage of the process is involved in a coagulation disorder.

I propose to confine myself to disorders of the first stage of the process—those in which impaired thromboplastin generation is associated with a normal one-stage prothrombin time. The most important of these are the two congenital deficiency diseases: hæmophilia and Christmas disease. I wish to consider two other causes of impairment of this early phase of blood coagulation: (i) circulating anticoagulants and (ii) functional platelet deficiencies.

(i) *Circulating anticoagulants.*—The great majority of those naturally-occurring anticoagulants whose mode of action has been fully investigated, appear to act by interfering with the formation of blood thromboplastin, and probably by inhibiting the reaction between antihæmophilic globulin (AHG) and the Christmas factor (Hougie and Fearnley, 1954). They have been observed in three groups of individuals—patients with hæmophilia or Christmas disease; young women following pregnancy, usually within the succeeding twelve months; and a miscellaneous group of elderly people of both sexes, most of whom suffer from some other chronic disease.

The pathogenesis of these anticoagulants is obscure; there is some evidence (Craddock and Lawrence, 1947; Frommeyer *et al.*, 1950) to suggest that the anticoagulants in the hæmophilic group are true antibodies to AHG, formed in response to its repeated therapeutic

administration, and it has been suggested that the anticoagulants in the other types of case may be iso- or auto-antibodies, though this has never been substantiated.

Clinical Diagnosis

In the hæmophilic group, the history does not differ from that of the uncomplicated disease, but in the others, the story is one of the recent onset of a spontaneous bleeding disorder in adult life, with no family history of such a condition. Spontaneous hæmatomata, intestinal hæmorrhage and hæmaturia are amongst the commonest features; hæmarthroses are rare, and purpura does not occur.

Laboratory Diagnosis

In these patients, as in hæmophilia, the whole-blood clotting time is usually prolonged, and the prothrombin consumption impaired, whilst the one-stage prothrombin time and platelet count are normal. If the patient is a woman, this combination of findings is practically diagnostic of the presence of a circulating anticoagulant.

The positive distinction from hæmophilia and Christmas disease depends on the fact that blood containing an anticoagulant not only fails to clot normally itself, but interferes with the coagulation of normal blood to which it is added. This effect may be demonstrated by the use of a variety of techniques. The simplest but the least sensitive of these consists of adding a small proportion of the patient's blood, plasma or serum to normal blood, and determining its effect on the clotting time. A typical result of such a test is shown in Table II.

TABLE II.—DEMONSTRATION OF AN ANTICOAGULANT IN SERUM

Normal blood (ml.)	1·0	1·0	1·0
Patient's serum (ml.)	0·1	—	—
Normal serum (ml.)	—	0·1	—
Normal saline (ml.)	—	—	0·1
Clotting time (min.) (mean of 3 readings).	20	5	8

A more sensitive indication of the presence of such an inhibitor may be obtained by the use of a similar modification of the prothrombin-consumption test, or of the thrombin-generation test (Fig. 1).

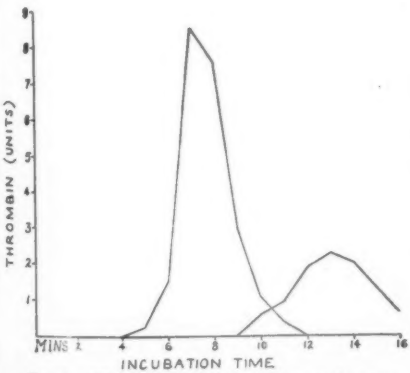


FIG. 1.—The effect of a circulating anticoagulant on the thrombin generation of normal blood. The left-hand curve shows the thrombin produced during the spontaneous coagulation of normal whole blood in glass. The right-hand curve shows the thrombin produced in the same normal blood to which one-tenth of a volume of plasma containing a circulating anticoagulant had been added.

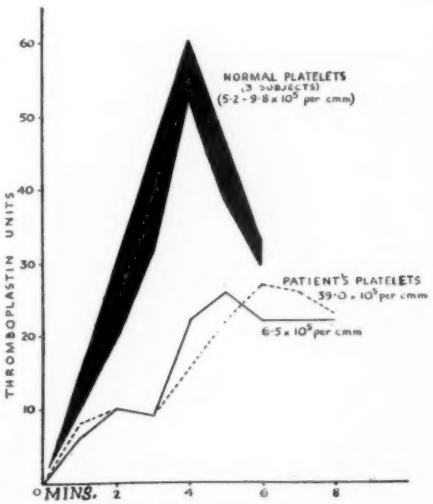


FIG. 2.—Thromboplastin-generation curves obtained by incubating the platelets from a case of hæmorrhagic thrombocythæmia, and from three normal subjects, with the same alumina plasma serum and calcium chloride. (After Fig. 7B from Hardisty and Wolff (1955), by kind permission.)

The thromboplastin-generation test (Biggs and Douglas, 1953) provides the most sensitive method for the detection of circulating anticoagulants. In this test, the patient's alumina-plasma and serum are nearly always both found to be deficient, distinguishing the condition from both hæmophilia and Christmas disease, in each of which only one of these reagents is at fault (Table III). Indeed, if the anticoagulant develops in the course of one of these

TABLE III.—RESULTS OF THE THROMBOPLASTIN GENERATION TEST IN VARIOUS CONDITIONS CHARACTERIZED BY A NORMAL ONE-STAGE PROTHROMBIN TIME

Diagnosis	Alumina plasma	Serum	Platelets
Hæmophilia	Deficient	Normal	Normal
Christmas disease	Normal	Deficient	Normal
Circulating anticoagulant	Deficient (inhibitory)	Deficient (inhibitory)	Normal
Qualitative platelet deficiency	Normal	Normal	Deficient

diseases, the double defect may make the diagnosis of the underlying condition impossible. Moreover, the patient's plasma or serum can be shown to inhibit the formation of thromboplastin in a normal system, though it is incapable of neutralizing preformed thromboplastin. The titre of the anticoagulant may be determined by finding the highest dilution at which the patient's plasma or serum will inhibit thromboplastin formation.

(ii) *Functional platelet deficiencies.*—A disorder of thromboplastin generation may be due to a deficiency of the thromboplastic principle of the platelets. Such a deficiency has been shown to be a feature of certain cases of non-thrombocytopenic purpura, notably hæmorrhagic thrombocythæmia (Hardisty and Wolff, 1955). This condition appears to be a type of primary myeloproliferative disorder in which an abnormally high platelet count is associated with spontaneous bleeding, particularly from the nose and upper alimentary tract. In many cases, the onset has been related to splenectomy, and there seems little doubt that a loss of splenic function plays a part in the ætiology of the condition.

The bleeding time is often increased, and the platelets are very abnormal in appearance, but there appears to be no gross abnormality of the coagulation process. Comparison of the platelets from these cases with those of normal subjects by means of the thromboplastin-generation test, however, reveals a qualitative abnormality, as shown in Fig. 2. A similar platelet defect has been demonstrated in several cases of purpura associated with a normal platelet count (Hardisty, 1952; Soulier *et al.*, 1955), and it is to be hoped that the use of this test may help in disentangling that peculiarly ill-assorted group of conditions, the functional platelet deficiencies, or thrombasthenias.

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Dr. Peter Wolf (Lister Institute of Preventive Medicine):

The Minimization of Variables in Clotting Experiments

While investigating inconsistencies in clotting experiments, I studied the variations produced in the thrombin-generation and other two-stage clotting tests by different batches of fibrinogen. Fig. 1 shows the widest variation obtained in the thrombin/fibrinogen clotting time, with eight different batches of fibrinogen, when plotting the reciprocal of the clotting time, $\times 1{,}000$ against the Owren thrombin units/ml. of thrombin solution used. It can be seen that the deviation from the straight line joining the origin with the 15 seconds clotting time is not significant for clotting times between 12 and 80 sec. and therefore calibration of freshly made or freshly reconstituted freeze-dried fibrinogen does not seem to be necessary.

Storage of fibrinogen, however, produces changes in reactivity. Fig. 2 shows the fall in reactivity of a fibrinogen solution after forty-eight hours storage at 4° C. compared with a freshly reconstituted sample from the same batch. This is best demonstrated by plotting the concentration of thrombin solution used against the reciprocal of the clotting time $\times 1{,}000$ (and of course the higher the reciprocal of the clotting time for any given thrombin concentration, the greater the reactivity). The fall in reactivity is progressive, and sometimes after three or four days and always ultimately, clotting with thrombin occurs in two stages. There are two distinct end-points, first a floccular clot followed later by a typical gelatinous clot. This change occurs more quickly if the fibrinogen is incubated overnight at 37° C.

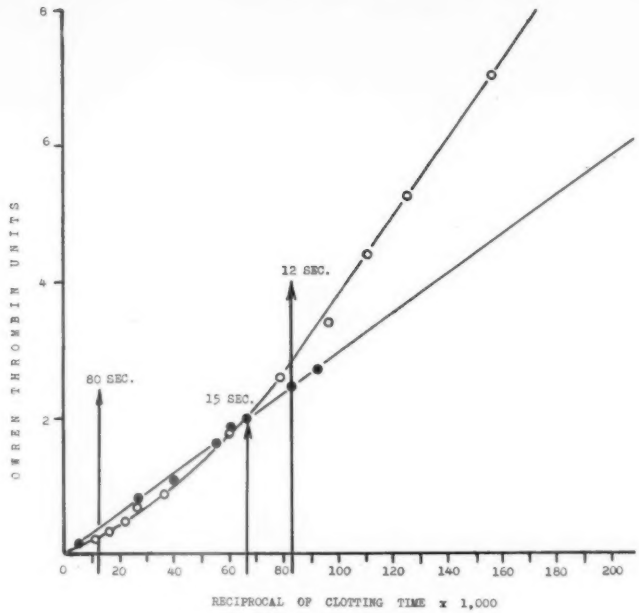

FIG. 1.—Fibrinogen calibration.

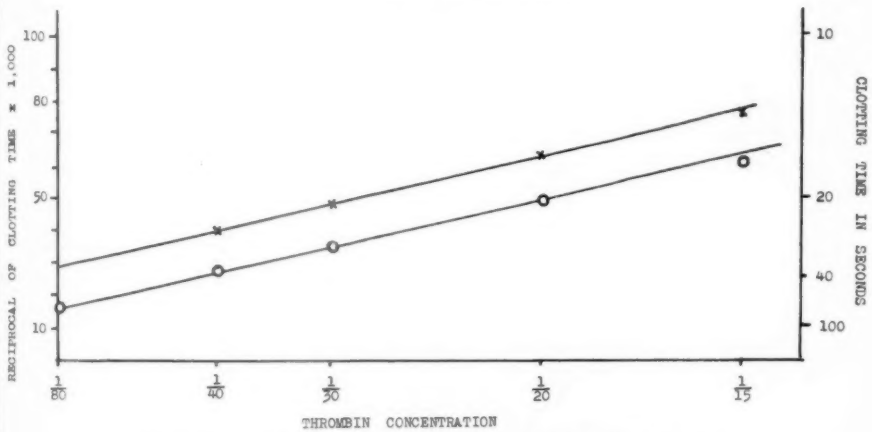

FIG. 2.—Loss of reactivity of a fibrinogen solution on storage at 4° C.
X = freshly reconstituted solution.
O = stored solution (48 hr.).

Fig. 3 illustrates these two clotting times. It is worth noting that the first-stage clotting time was approximately the same, but never shorter than that of the parent fibrinogen. For fibrinogen stored at −10° C. there is a variable drop in reactivity on freezing but no further loss on storage. These experiments demonstrate that, for accurate work, comparison of results using fresh or freshly reconstituted fibrinogen with those using stored fibrinogen is not justified.

Modifications of the thrombin-generation test were tried in order to minimize the variations produced by different fibrinogens, and by the non-uniform platelet content of plasmas. Also, it was desirable that this modification should give a measure of the rate of prothrombin

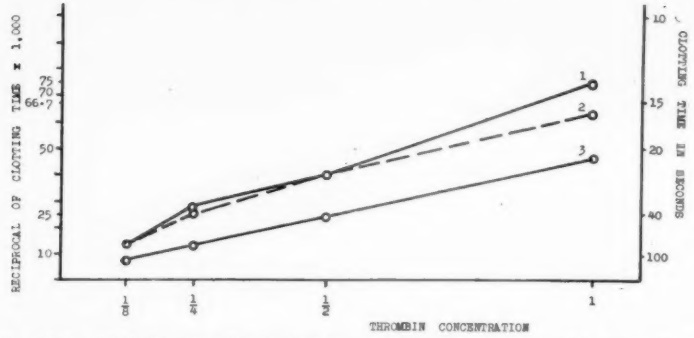

FIG. 3.—Reactivity of fibrinogen after twelve hours' incubation. (1) Freshly reconstituted. (2) Incubated: 1st-stage floccular clotting. (3) Incubated: 2nd-stage gelatinous clotting.

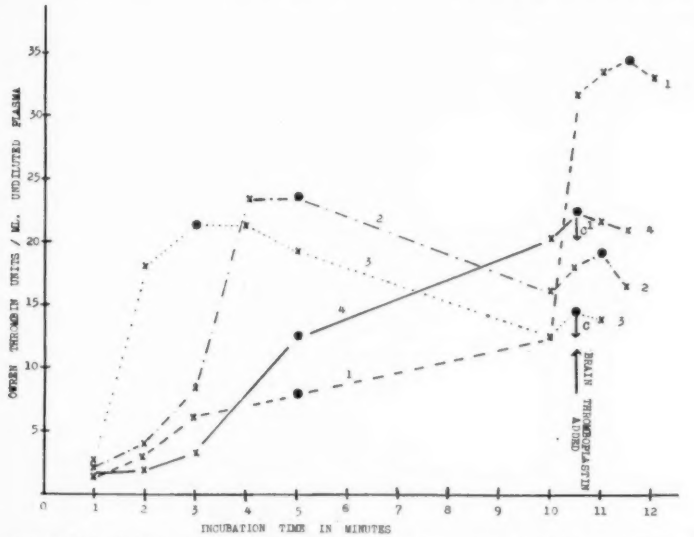

FIG. 4.—Effect of high platelet concentrations on the conversion ratio of a highly centrifuged plasma.

Highly centrifuged plasma	No. of platelets/c.mm. in reaction mixture	Equivalent count/c.mm. of undiluted plasma	Conversion ratio
1	0	0	8/34·2 = 0·23
2	25,000	500,000	23·4/19 = 1·23
3	50,000	1,000,000	21·2/14·4 = 1·47
4	250,000	5,000,000	12·4/22·2 = 0·56

●Points from which conversion ratios are derived.

conversion irrespective of the prothrombin content, and provide a simpler method of expressing the results than by the comparison of graphs. The determination of the prothrombin conversion ratio (Wolf, 1956), which will be described, is a method which was developed to overcome these difficulties. The ratio is:

$$\frac{\text{The maximum quantity of thrombin produced by a material within 5 min. of recalcification}}{\text{The maximum quantity of thrombin found on addition of brain thromboplastin after a further 5½ min. incubation}}$$

These quantities are measured in thrombin units/ml. of undiluted plasma. Plasmas

prior to testing are rendered virtually platelet-free by centrifugation; then, after dilution with veronal buffer, a fixed quantity of platelet suspension or platelet substitute is added.

The data from which this ratio is derived are demonstrated in Fig. 4. This series of experiments on the same diluted plasma is given as an example of the type of information obtained from the conversion ratio. In Experiment 1, a plasma was tested free of platelets, when the conversion ratio was given by 8/34·2, which is 0·23. Experiments 3 and 4 demonstrate the usefulness of this ratio in recording early or late onset of prothrombin conversion in cases where prothrombin conversion is nearly complete in 10 min. High values of the ratio are given by early and complete conversion with calcium chloride. In both experiments the amount of thrombin produced by the brain thromboplastin (C and C[1]) is of the same order, but the earlier prothrombin conversion in Experiment 3 is shown in the higher conversion ratio of 1·5 compared with a value of 0·56 in Experiment 4. This difference is due to the fact that in Experiment 3, where earlier conversion occurs, the total thrombin content of the mixture begins to fall after 3 min., due to the anti-thrombin effect outbalancing the rate of thrombin formation, so that at 10 min. the thrombin level has fallen considerably. Although the same amount of thrombin is liberated with brain thromboplastin as in Experiment 4, the total thrombin content at this point is considerably lower than in Experiment 4 and this raises the ratio.

In my opinion the prothrombin conversion ratio retains the sensitivity of the thrombin-generation test, and yet has the advantage of giving the result as a simple numerical index, and minimizing the other variable factors previously mentioned. This test is versatile and has been the basis of most of my subsequent investigations.

The largest single variable factor in clotting experiments is produced when platelet-containing plasma is stored in the refrigerator. In view of the magnitude of this variation it is surprising that there is so little reference to it. Fig. 5 shows a typical example: a platelet-

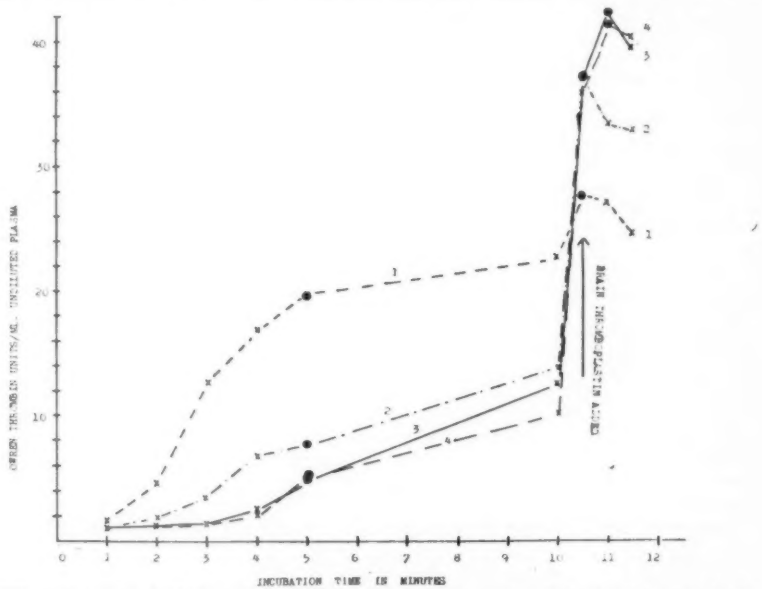

FIG. 5.—Effect of storage at 4° C. on the prothrombin conversion ratio of platelet-rich and platelet-free plasma.

	Conversion ratio
(1) Unspun plasma 18 hrs. at 4° C. after venipuncture ..	0·72
(2) Unspun plasma 3 hrs. at 4° C. after venipuncture ..	0·21
(3) Spun plasma 3 hrs. at 4° C. after venipuncture	0·11
(4) Spun plasma 18 hrs. at 4° C. after venipuncture	0·12

●Points from which conversion ratios are derived.

rich plasma was obtained from citrated blood stored at 4° C. for three hours after venipuncture. The conversion ratio is given by 0·2, but after a further eighteen hours' storage of this

separated plasma at 4° C., the conversion ratio rose to 0·7, showing approximately a three-fold increase in this time. The thrombin generated in the first five minutes also demonstrates this remarkable increase in the rate of prothrombin conversion.

Plasmas containing as few as 5,000 to 10,000 platelets/c.mm. show a significant increase in the conversion ratio on storage. After eighteen or twenty-four hours' storage there is usually no further significant increase in the ratio, much longer storage producing a gradual, slow decrease. The freezing of a platelet-containing plasma also produces this activation, but longer storage is required to reach maximal activity.

These changes do not occur on storage of platelet-free plasmas, either frozen or at 4° C. Fig. 5 shows samples of the platelet-free plasma after storage for three and eighteen hours (Experiments 3 and 4), when the conversion ratios of 0·11 and 0·12 show no significant change, and it can be seen that the operative points lie very close. Nor was any significant difference obtained when these plasmas were subsequently tested after addition of platelet suspension or platelet substitute. Therefore it seems necessary for consistent results to obtain platelet-free plasma from citrated blood without an intermediate period of storage, and to add a prepared platelet suspension or substitute before performing conversion tests. Also, comparison of thrombin generation or prothrombin consumption on platelet-containing plasmas is only valid if all specimens are tested after the same interval since venipuncture. Only a platelet-free plasma, therefore, may be frozen as a reference standard; even this is not absolutely stable, but shows a gradual decrease in the conversion ratio due to falls in Factor V and Factor VII activity. Adoption of these measures has eliminated a lot of apparently unaccountable variations in the measurement of prothrombin conversion. I think these effects are the same as those described by Hougie (1955) for platelet-containing plasmas which had been incubated at 37° C.

The use of platelet substitute has further minimized variation in prothrombin conversion tests. Using platelet suspensions, comparison of results done at intervals of months becomes impossible, because a different set of results is obtained with each batch of suspension. Initially I used an ether extract of platelets, but since the paper of Bell and Alton in 1954 I have found chloroform extract of acetone-dried human brain more convenient. The extract is suspended in veronal buffer and stored at 4° C., and is suitably diluted for use in clotting tests.

Both high and low concentrations of the extracts produce slow prothrombin conversion when added to platelet-free plasma, and there is an intermediate dilution at which conversion is maximal, the change in activity being gradual. The concentrated extract slowly deteriorates on storage and progressively less dilution is required over a period of time for maximal activity, and therefore the concentrated extract has to be recalibrated at intervals.

Substitution of extracts for platelets could be made without discrepancy in normal, Factor-V- and Factor-VII-deficient plasmas, hæmophilic plasmas and plasma from Christmas disease. In a heparin-containing system, however, platelet suspensions give a much quicker conversion than any of the extracts, because of a powerful anti-heparin effect produced by platelets for which the presence of plasma was found to be essential.

To avoid confusion this anti-heparin activity is used in the specific sense that the addition of a platelet suspension to a heparinized, platelet-poor plasma shortens considerably the clotting time of the plasma fibrinogen when a thrombin solution is added, but in the absence of heparin a platelet suspension has no influence on the speed of the thrombin/fibrinogen reaction. No anti-heparin effect was detected in any of the extracts, since they did not influence the thrombin/plasma-fibrinogen reaction, either with or without heparin.

Finally, it should be mentioned that to obtain consistent results in estimating Factor VII by the method of Owren and Aas (1951), it has been found necessary to incubate the plasma thromboplastin mixture for 10 min. before adding the calcium chloride, since progressive shortening of the clotting time occurs up to this point.

My thanks are due to Dr. R. A. Kekwick, in whose department this work was done, and for which a grant was received from the Medical Research Council.

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Section of Medicine

President—G. E. BEAUMONT, M.A., M.D., F.R.C.P., D.P.H.

[*November* 22, 1955]

DISCUSSION ON CERVICAL SPONDYLOSIS

Sir Russell Brain:

Incidence.—Cervical spondylosis is a major cause of serious disability. During the years 1953–55, 70 in-patients admitted to the Neurological Department of the London Hospital had cervical spondylosis as one of their main diagnoses, and comparatively few of these were admitted on account of symptoms which were purely radicular. Before we can say that the frequency of this disorder is increasing we must take account of its more frequent recognition and of the fact that there are more older people in the population. Nevertheless, there appears to be some evidence that it is commoner than it was even twenty-five years ago.

Ætiology.—Its ætiology is complex. It seems probable that in some patients some general degenerative process involving the intervertebral discs is important, for we sometimes meet with spondylosis at all levels of the spine, and there are patients who suffer from the symptoms of cervical and lumbar disc lesions either consecutively or even simultaneously. Such a degeneration seems to be related to the metabolic processes of ageing. The occurrence of degeneration of a single intervertebral disc, however, suggests that some factor other than a general degenerative process must often be present. It is natural to enquire whether this may not be trauma. A history of an important head injury will not be obtained in more than 25% to 30% of patients suffering from cervical spondylosis, and even in those cases we do not know whether the trauma initiated or merely exacerbated the disc lesion. If, however, the injury which starts a disc degeneration may have been slight and have occurred many years previously, perhaps in childhood, it is not surprising that no history of it should be obtained. There seems to be evidence that occupational trauma may play a part in deciding the localization of spondylosis.

Apart from external trauma we have to consider the possible importance of the normal wear and tear of the extremely mobile cervical spine. It is noteworthy that cervical disc degeneration is almost always present adjacent to a congenital abnormality such as fusion of two cervical bodies, which suggests that the additional wear and tear on neighbouring articulations caused by such a lesion is an ætiological factor. Thus any account of the ætiology of cervical spondylosis should take account of both local and systemic factors, the relative importance of which doubtless varies from patient to patient.

The nature of a disc protrusion.—The mere fact that an intervertebral disc protrudes does not in itself throw any light upon how this is brought about. I believe that this may occur in either of two ways. The first is a nuclear herniation. This occurs as a result of rupture of the annulus fibrosus through which part of the nucleus pulposus protrudes. This may be the result of trauma or it may occur spontaneously without any history of injury or undue stress. The second cause of a disc protrusion is disc degeneration. When an intervertebral disc degenerates it tends to provoke increased bone formation from the adjacent portions of the bodies of the vertebræ, particularly posteriorly. The result is apt to be a posterior osteophyte which is composed partly of bone, partly of fibrous tissue and partly of cartilage. However, such an osteophyte does not always occur when a disc degenerates. Thus in the cervical spine two adjacent discs may be degenerated but only one of them is the site of an osteophyte. It follows from this that mere narrowing of the discs, as seen in the lateral X-rays of the cervical spine, does not in itself indicate the presence of an osteophyte.

X-ray appearances.—While narrowing of a cervical disc, when seen in the lateral X-rays, is naturally of importance, it may not be associated with posterior osteophyte formation. On the other hand such an osteophyte may be present with little evidence of disc narrowing, and, in particular, with no evidence of anterior osteophyte formation. The point to which special attention should be directed is increased density of the angles of the bodies adjacent to the posterior part of the disc, and, in particular, a projection of these bodies into an opaque bulge extending into the spinal canal. Myelograms show how much larger these posterior osteophytes often are than had been suspected from the plain X-rays. In another type of case gross narrowing of disc spaces is associated with gross anterior and posterior osteophytes.

The site of disc protrusions.—Intervertebral disc protrusions in the cervical region occur at three main sites. A median projection tends, if it is large enough, to compress the spinal cord in the middle line and may thereby interfere with the circulation through the anterior spinal artery. A postero-lateral protrusion may compress the spinal roots within the spinal canal against the corresponding lamina. A foraminal protrusion is so-called because it projects into the intervertebral foramen, and may compress the spinal roots there. Since

the lower cervical spinal segments are situated not opposite their corresponding vertebræ but opposite the one above, the lower cervical spinal roots run an oblique course to reach their corresponding foramina. It follows that, as in the case of the lumbar roots, the lower cervical spinal roots may be compressed either by the intervertebral disc at the level at which they leave the spinal cord or by the one below when they are passing through their foramen. This is one explanation of the apparent discrepancy between the level of the disc change as seen in the X-rays and the segmental level of the symptoms. It has also been pointed out that as disc degeneration in the cervical spine tends to shorten the spine at that level, whereas the spinal cord remains the same length, it may lead to pressure upon the lower cervical roots within foramina which are anatomically normal.

Referred pain in cervical spondylosis.—It should be borne in mind that a single cervical spinal posterior root innervates not only its corresponding segmental cutaneous area or dermatome, but also muscles, bones, joints, ligaments and even viscera, which may be remote from the corresponding dermatome. Thus, for example, the seventh cervical root supplies not only a cutaneous area extending down the upper limb usually to the middle finger, but also a number of muscles including pectoralis major, triceps, serratus magnus, and latissimus dorsi. Hence pain caused by irritation of this spinal root may radiate widely to the front and back of the chest, and so simulate pain of cardiac origin.

Differential diagnosis.—A number of diagnostic problems may arise in connexion with cervical spondylosis. Broadly, they fall into three groups. First, the symptoms of cervical spondylosis simulate those of some other disorder. The simulated disease may be visceral, as in a case of the cardiac pain which I have just mentioned. It is now well recognized that the neurological symptoms of cervical spondylosis may simulate a large variety of nervous disorders, commonest of which are disseminated sclerosis and motor neurone disease. Secondly, since cervical spondylosis is a very common disorder, it may coexist with some other condition, which is the real cause of the symptoms. Thus, a patient may have angina of effort and also cervical spondylosis, in which case the cervical spondylosis may be regarded as the cause of the pain, which is really cardiac in origin. Similarly cervical spondylosis may coexist with independent organic nervous disease, such as spinal tumour, disseminated sclerosis or subacute combined degeneration, and so give rise to confusion. Lastly, some other disease of the cervical spine may simulate cervical spondylosis and is especially liable to give rise to difficulty if it is itself associated with organic nervous disease. Examples of this are arthropathy of the cervical spine associated with syringomyelia or, much more rarely, with tabes dorsalis.

Cervical spondylosis associated with œsophageal symptoms.—I recently saw a patient in whom cervical spondylosis had been discovered in the course of a barium swallow, because the anterior osteophytes were large enough to distort the œsophagus. Since then I have seen a few patients in whom œsophageal symptoms, usually predominantly sensory in character, were associated with cervical spondylosis, and the possible relationship between the two is being further investigated.

Dr. W. Ritchie Russell:

Painful neuropathies affecting the upper limbs, neck and posterior scalp form a large part of the neurological out-patient work of a general hospital; in Oxford, for example, we see about 130 such patients every year, i.e. 10% of the total new patients. These neuropathies are a disorder especially of middle age, and are most common in women, so much so that we often refer to them as cases of "Housewives' neuritis". Many of them have a degree of cervical spondylosis, but the influence exerted by the spinal condition is often conjectural.

Many of us remember the various fashions through which the subject of the brachial neuropathies has passed—the cervical rib, the large transverse process, the high first rib, the narrow costo-clavicular space, the tight scalene muscles, and so on. And we must beware lest in turning our attention too much to the newer conceptions of cervical spondylosis, or even the carpal tunnel syndrome, we are guilty of over-simplifying a complicated problem. There still is a regrettable tendency among some clinicians to turn first to X-ray examinations in order to find the explanation of these neuropathies. Neurologists will agree with the dangers of such an attitude, and this is especially the case with cervical spondylosis for which radiological evidence is to be found in a high proportion of symptomless people.

Certainly the clinical method comes into its own in this condition, for the accessory methods are comparatively unhelpful. It is important, therefore, to consider critically the symptoms in cases of brachial neuropathy in order to attempt to explain the various factors involved.

The first point to emphasize is that the symptoms of brachial neuropathy are rarely those one would expect from simple pressure on either a nerve or nerve root. Such pressure on a mixed nerve is usually a painless affair, even to the degree of complete numbness and

paralysis. In the brachial neuropathies on the other hand, as in sciatica, anæsthesia and paralysis are rare, while pain is often by far the most important symptom, indeed it is often the only symptom of importance. Further, the pain, when it occurs, is not often referred like a root pain to the periphery of the limb. On the contrary, it is often most severe in the more proximal part of the limb, and is associated with tenderness of muscles and nerve trunks. There is often also a striking intolerance of the main nerves to stretch—as is best seen in the straight leg-raising test in cases of sciatica.

As Gowers pointed out last century, nerve conduction in these cases of what were then called brachial neuritis, is unduly vulnerable to slight compression of the limb such as may occur by the weight of the body during sleep. Ischæmic cuff tests on the affected limb also lead to this unduly quick development of numbness in the fingers. Tapping over the nerve trunks as in Tinel's sign is sometimes instructive, for it may, over a limited part of the course of the nerve, cause sudden neuralgic-like sensations at the peripheral distribution of the nerve. This presumably indicates a level at which conducting nerve fibres are in a specially abnormal state. This may often be demonstrated in cases of the carpal tunnel syndrome on tapping over the median nerve at the wrist. Similarly when a cough causes a root pain it may be concluded that the nerve fibres at the root level are in an abnormally sensitive state.

How then can cervical spondylosis lead to the varied clinical picture of a painful neuropathy in the shoulder girdle, arm, forearm and hand? The first point to re-emphasize is that tenderness of peripheral nerve trunks causing local pain must depend on an abnormal state not of the transversing nerve fibres but of the nerve sheath. The clinical evidence in these cases of the main lesion being in the nerve sheaths is, I think, pretty conclusive, and there is, of course, plenty of pathological evidence of the irritating effect of the spondylotic lesions on adjacent nerve root sheaths. Frykholm's beautiful studies of root-sleeve fibrosis (1951, *Acta chir. scand.*, **101**, 345) are specially important in this regard, and I would add the astonishing adhesions which may develop around the cauda equina in close relation to a prolapsed disc. This in many respects looks more like the effect of a chemical irritant than of friction. Further, the fact that nerve sheath tenderness may develop throughout the whole length of the peripheral nerves raises the possibility of a chemical effect spreading distally along the nerve in the endoneural spaces.

Another important factor depends on the fact that root sleeve fibrosis involves loss of root elasticity. In a limb which is being used (and brachial neuropathies develop in active people) this localized loss of elasticity involves an extra stretch to the more peripheral segment. This may lead to sheath trauma and pain and spreading loss of elasticity until a vicious cycle develops, and like a row of ninepins each affected nerve segment leads to collapse of the next until the whole of the neural tree to the periphery has tender, painful and inelastic nerve sheaths. No wonder then that rest to the limb with the elbow supported is an essential part of conservative treatment for these cases. My contention, therefore, is that the symptoms of neuropathy in relation to cervical spondylosis are largely due to changes in the nerve sheaths, which when added to the resulting loss of elasticity form the essential background to the mechanisms involved.

From this we may take another and significant step, for if a peripheral nerve becomes inelastic, it also becomes so vulnerable to stretch that gross peripheral nerve lesions may then be caused by the stretching effect of normal range of limb and joint movements. This, I think, is the mechanism of the palsies in shoulder-girdle neuritis, and may also play an important role even in the carpal tunnel syndrome. Extension of the wrist while the elbow is extended involves severe stretching of the median nerve at the wrist, so we may come to the surprising conclusion that the carpal tunnel syndrome may depend partly on the effects of cervical spondylosis. Certainly many cases of carpal tunnel syndrome also have cervical spondylosis. Similarly, an apparently clear case of median nerve neuritis at the wrist may develop pain more proximally in the arm and forearm of a nerve sheath variety, and to explain this there is no need to look for spinal segmental overlappings, but only the anatomical continuity of one part of the brachial plexus with another by which loss of elasticity of one part may result from purely physical factors, in similar changes occurring at other levels.

Local areas of muscle spasm and pain may also, of course, come into the picture of brachial neuropathy in a more segmental way, for deep muscle pain is referred extensively; we are all familiar with the type of patient who gets relief of arm pain from a procaine injection into a tender muscle medial to the scapula.

The general inference from these views on the subject is that pressure on the nerves and nerve roots is not, in itself, the cause of the painful neuropathies. The pain depends on the development of a neuritis or radiculitis in which the important changes are in the nerve sheath, and, in practice, the treatment of this neuritis is often more important than are attempts to treat the cervical spondylosis directly. Thus the occupational stresses of the busy housewife are particularly liable to aggravate the condition, and these cases are often most effectively handled if they can be admitted to hospital for two weeks of physical rest

with light neck traction (5–8 lb.) while lying in bed for several hours each day. The old form of traction by a pulley system from the ceiling is a dangerous method which should not be used.

In discussion Dr. Russell said that he used traction as a form of treatment only in some cases with associated neuropathies. When the cord is involved, neck fixation is often effective, and if wearing a collar is not followed by some improvement the diagnosis should be reconsidered. With regard to psychological factors, the obsessional housewife is much more likely to give herself a neuropathy by doing too much.

He was surprised to hear some surgeons advocating operation in these cases with so much confidence; he felt that with longer experience they would become more hesitant.

Dr. Henry Miller:

Perhaps the most striking thing about cervical spondylosis is the avidity with which the term and the syndrome have been so widely adopted. It is after all only a very few years since Sir Russell Brain first described the condition. He performed an invaluable service in describing with his usual clarity the neurological signs encountered in association with it, and a lesser one in leading us to adopt a new name for the skeletal condition previously long familiar as cervical osteoarthritis. The value of this terminological advance seems to me dubious. It certainly indicates the degenerative as opposed to the inflammatory basis of the condition, but it does not stress the real progress in our understanding of the disease which is implied in the central position now accorded to the intervertebral disc in the pathogenesis of these osteoarthritic changes. At any rate the term cervical spondylosis has apparently come to stay, and it is a sobering reflection that practically every out-patient clinic and every medical ward in the hospital now contains at least one example of a disease which had not even been invented ten years ago. Obviously the concept has filled a yawning diagnostic gap.

I wish to make only three points. First, it must be constantly borne in mind that cervical spondylosis is essentially a radiological diagnosis, depending on physical signs encountered on a radiograph. When we realize that such physical signs are the rule rather than the exception in the X-ray plates of all middle-aged and elderly patients, the significance of such radiological evidence is clearly limited. The radiological changes of cervical spondylosis seem, in fact, to be merely a sign of middle age perhaps somewhat more reliable than the finding of grey hair. There would seem indeed to be a logical case for selecting for ætiological investigation the 20% of men over 50 *without* cervical spondylosis rather than the 80% of what we may call normal controls whose X-rays show signs of the disease.

It is clear that in the large majority of patients with radiologically significant cervical spondylosis, the condition is quite asymptomatic. A considerable number of cases have occasional stiff neck. A sizeable proportion have asymptomatic neurological signs indicating minor lesions of nerve roots or involving the long tracts of the spinal cord. A few patients have trivial neurological symptoms such as tingling in the fingers or occasional numbness in the legs; and a very few develop more or less disabling syndromes referable to root or cord damage. It is evident that the ubiquitousness of these X-ray changes calls for special caution in the attribution of ætiological significance.

A few years ago the error mostly to be feared was to label as disseminated sclerosis a patient suffering from featureless paraparesis or quadriparesis which was, in fact, due to cord compression from a disc lesion. This mistake is still by no means unknown. It is especially serious for the patient, in that it may deny him the real possibility of dramatic and complete relief of a grave disability by surgical treatment. It is especially troublesome also for the doctor, who may be faced with the difficult choice of leaving such a treatable lesion undetected, or of exacerbating the condition of a patient with disseminated sclerosis by myelography.

With the increasing appreciation of cervical spondylosis, however, and the widely varying neurological syndromes which are undoubtedly encountered in association with it, there can be little doubt that, at any rate in hospital circles, the pendulum has swung in the opposite direction, and many neurological diseases are attributed to spondylotic changes recognized on an X-ray film which are subsequently shown by more informed assessment to be quite coincidental. Within the last year or two there must be few physicians who have not encountered cases of syringomyelia in which the radiological finding of cervical spondylosis has blinded a previous observer to a widespread change in superficial sensation indicating that pain down the arm was due to a syrinx. In the same way it is easy to attribute slight unsteadiness on the feet and tingling in the finger tips to similar findings in an elderly patient without carrying out special tests to exclude early subacute combined degeneration of the cord. After all, the most important mistake in medicine is to miss something which is really treatable. Many patients continue to suffer from pain and tingling in the hands associated with a spondylotic X-ray who could be rendered comfortable

by the simple operation of decompressing their carpal tunnels. By comparison, the 15-year survival of patients diagnosed as suffering from progressive muscular atrophy usually does nobody any harm—except for the occasional candidate who encounters such an unrecognized case of spondylitic myelopathy in a professional examination. Similarly, to mistake some other extrinsic cord tumour for spondylotic compression of the cord is an error which can be remedied at operation. A more unexpected mistake, but one which I have encountered twice in recent months, is to misinterpret the significance of nuchal pain and asymmetrical spasm of the cervical muscles, and to treat a posterior fossa tumour by immobilizing the neck. It must be remembered also that by reason of their common age incidence the pains of cardiac ischæmia, Pancoast's tumour, or pericapsulitis of the shoulder joint (frozen shoulder) usually occur in patients who also have cervical spondylosis, and afford wide scope for diagnostic error based on the acceptance of radiological evidence at its face value.

The lesson of these observations is surely this: X-rays must be carried out in every case presenting evidence of a cervical cord or root lesion, but their main purpose is to exclude bony metastases or tuberculosis. The diagnosis of spondylotic radiculopathy or myelopathy should be based on history and physical signs, and not on the finding of radiological changes which are so ubiquitous as to be valueless. Careful physical examination will reveal that the case of spondylitic myelopathy masquerading as motor neurone disease shows none of the characteristic over-briskness of the jaw-jerk, but almost invariably exhibits some degree of impairment of vibration sense in the lower limbs never encountered in the purely motor disease. In the case of subacute combined degeneration, a glossy tongue and tender calves will usually permit a correct diagnosis even before special tests are carried out; while when tingling in the fingers is due to cervical spondylosis it is usually asymmetrical, involves fingers other than those supplied by the median nerve, and is commonly associated both with actual disappearance or blunting of some of the deep reflexes of the upper limb and selective œstophytic encroachment on the appropriate intervertebral foramen.

Secondly I would again mention the importance of trauma in the syndrome of cervical spondylosis. I am referring less to gross trauma, or to the postural trauma which has recently been described by Sir Charles Symonds as producing a catastrophic cord lesion in the spondylotic patient, than to the effect of the minor traumata which are often enough to convert an asymptomatic condition into a troublesome disability. In my own practice the car driver whose vehicle is run into from behind, or the underground miner who strikes his head on a low roof, are the two commonest such incidents, in either of which the cervical lesion may be over-shadowed at first by a concurrent head injury. On such occasions considerable pain in the neck and down the arm may follow, with or without neurological signs, and as in most such cases where compensation is involved, the disability is often much more prolonged than seems to be justified by any objective finding.

In relation to the effects of minor trauma of the "wear and tear" type in the ætiology of the actual skeletal changes of the syndrome, the initial results of a small pilot survey which we are carrying out in Newcastle may be of some interest. Amongst asymptomatic subjects, we have found that more than 90% of underground miners between the ages of 50 and 55 show radiologically significant spondylosis, and that in most of these cases the condition is severe by Sir Russell Brain's criteria. Similar changes were encountered in about two-thirds of sedentary male workers in the same age bracket, but in appreciably less than half of a group of similarly selected housewives. It is unlikely that a housewife's job today demands less physical exertion or is less traumatic than that of a clerk, a doctor, or a managing director, and these figures suggest the possibility of a sex difference in incidence irrespective of trauma.

Finally, I would with some trepidation draw attention to an apparent relation between painful syndromes associated with cervical spondylosis, and emotional disturbances. There seems to be little doubt at least that these physical symptoms—and I refer in particular to brachial neuritis due to root compression—are often encountered in association with or are followed by frank emotional illness. The commonest association is with an agitated depressive psychosis with obsessive preoccupation, hypochondriasis, and sleeplessness. I believe that such a complicating psychiatric illness accounts for some of the excessive invalidism which one so often encounters in relation both to cervical and lumbar disc syndromes and for some of the failures of orthodox treatment. It is my impression also that this association is more frequent than can be accounted for by the coincidence of two conditions which admittedly have a similar age incidence.

The simplest interpretation of such a relation between brachial neuritis and agitated depression is of course that the patient develops his depression and agitation because of the pain. I do not believe this interpretation to be correct. It does not allow for the fact that the clinical features of an agitated depression are specific and distinct, and that this is a most uncommon reaction to pain of any kind. Furthermore, of course, the psychosis often occurs after the acute pain has cleared up. The second interpretation, which may well be

true to some extent, is that a tense and apprehensive patient seizes on and magnifies physical discomfort which would be ignored or treated as a trivial nuisance by a more stable subject or by the same subject in a more stable frame of mind.

There is, however, a third possibility, and one which I am inclined to think is important. The agitated patient is tense. The provocation of musculo-skeletal symptoms in spondylosis or other forms of bone and joint disease by cold is well known, and seems to be related to the increase in muscle tone which is produced on exposure to variable low temperatures. Is there any reason why the muscular tension which occurs in an agitated patient, and which is evident in tremor and exaggerated reflexes, may not similarly provoke symptoms and perhaps even definite lesions in the musculo-skeletal system? At any rate my experience is that it is not much use treating the disc without assessing and treating the patient, and that on at least some occasions the treatment of the latter renders that of the former unnecessary. I do not wish to go on record as suggesting that the correct treatment for cervical spondylosis is electro-convulsive therapy, but I have seen some superficially neurotic patients whose spondylotic symptoms, undoubtedly organic, and sometimes accompanied by appropriate physical signs, have completely resisted months of immobilization, but have been rapidly and permanently cleared up by a short course of ECT.

In conclusion, the interest aroused by this syndrome, and its current diagnostic popularity, should not blind us to the fact that, so far at any rate, it has probably been a source of more comfort to the doctor than to the patient. Not only does the former have the consolation of an elegant and satisfying hypothesis for the pathogenesis of those obscure cases of paraplegia in late middle life which were previously so difficult to place in the hospital diagnostic index. He is also spared trying to fit every such case into the unyielding framework of some progressive neurological system disease—and giving an appropriately grave prognosis subsequently belied by the patient's long survival. So far as effective therapy goes, however, the spondylotic patient has all too often gained little beyond the tonic effect of a more cheerful prognosis, and as he shifts uneasily in his plastic halter during the twelfth of those long and uncomfortable months which my orthopædic colleagues tell me are the *sine qua non* of effective stabilization of the cervical spine, he may be pardoned for wondering if he was really so much worse served as an uncommitted sufferer from paraplegia of late middle age, undiagnosed.

Mr. J. E. A. O'Connell:

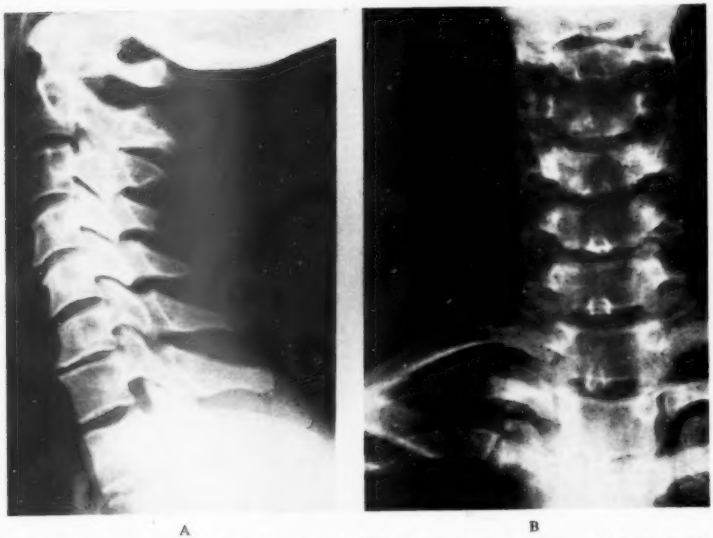
There are three aspects of the problem of cervical spondylosis which I wish to consider. The first concerns terminology and the second the cause of the disturbance of spinal cord function in these cases; thirdly an attempt will be made to evaluate surgery in the treatment of patients with myelopathy associated with cervical spondylosis.

In the publications concerned with cervical spondylosis it would seem that different writers attach different meanings to the same term. Thus one author (Muller, 1951) describes under the title of cervical intervertebral disc protrusion a series of cases treated surgically with little benefit or actual deterioration. A consideration of his records suggests that his cases were, in fact, examples of cervical spondylosis. His results should therefore not be accepted as indicating that surgery has little value in cases of cervical disc protrusion. Indeed, as will be indicated later, the reverse is the case. It seems that other authors describe both osteophytic outgrowths and masses of intervertebral disc tissue as disc protrusions (Brain *et al.*, 1952). The inclusion of cases of the latter type in a series of surgically treated cases of cervical spondylosis will exaggerate the benefits of surgery in cases of true spondylosis. I believe it is helpful to distinguish three types of lesions—(1) intervertebral disc protrusion, (2) secondary spondylosis, and (3) primary spondylosis.

(1) An *intervertebral disc protrusion* is a space-occupying lesion within the spinal canal composed of intervertebral disc tissue; it may be of annulus fibrosus alone or nucleus pulposus alone but usually it is composed of a combination of both annulus and nucleus. The essential cause of the development of such lesions is the internal pressure in the nucleus pulposus acting upon ligaments damaged in various ways but especially by trauma. The term "protrusion" has the advantage of including masses composed of either or both parts of the disc. It should, however, be confined to such masses and not used to include osteophytic outgrowths from the vertebral margins.

(2) The term *secondary spondylosis* is descriptive of the changes which develop in an intervertebral joint when there is a disc protrusion and they will therefore frequently be localized to a single level (Fig. 1A and B). They consist of narrowing of the interval between the vertebral bodies, sclerosis of the surfaces of these bodies adjacent to the affected disc and lipping of their margins—changes which may be made out radiologically and at operation. Such changes are not only of diagnostic importance but, as will be seen, carry therapeutic implications.

(3) The term *primary spondylosis* describes a group of degenerative changes of unknown causation. Not only are the joints between the vertebral bodies affected but also the



A B

FIG. 1 (A and B).—Secondary cervical spondylosis (C6–7) in a patient with cervical and brachial pain from whom a lateral cervical disc protrusion was excised.

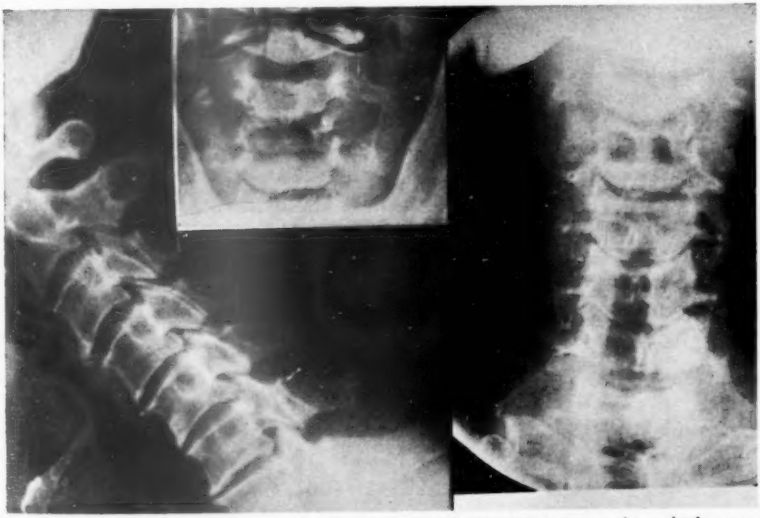


FIG. 2.—Primary cervical spondylosis. The involvement of the joints between the articular processes and the left atlanto-axial as well as those between the vertebral bodies is seen.

posterior joints between the articular processes and the changes are frequently not only severe but widespread (Fig. 2). Only exceptionally are intervertebral disc protrusions present. Here the arthritic vertebral margins, separated by degenerate disc tissue, form ridges across the floor of the spinal canal.

The cause of the disturbance of spinal cord function which may occur in association with primary spondylosis in the cervical region is clearly relevant to a discussion of therapy. One approach to this difficult problem is to consider the results of surgery in two types of lesion in the cervical portion of the spinal canal namely: (i) extramedullary tumour, and (ii) intervertebral disc protrusion.

(i) *Extramedullary spinal tumours.*—The extremely gratifying results which commonly follow the excision of these tumours are well known. Two examples may be cited.

Case I.—Mrs. M., aged 55, had an eighteen months' history of paræsthesiæ in the hands and occipital and cervical pain for nine months. Examination revealed a very mild spastic tetraparesis with minimal sensory disturbance. Myelography (Fig. 3) revealed a partial obstruction to the flow of dye opposite the second cervical vertebra and at operation the spinal cord was flattened and avascular where it lay across an anteriorly situated tumour. The growth proved to be a meningioma and following its excision the patient showed a rapid improvement and loss of focal signs.

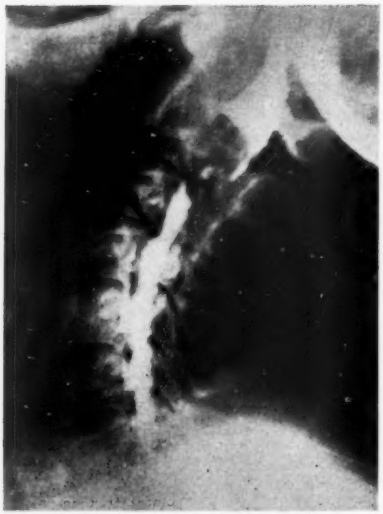


FIG. 3.—Myelogram of Case I. The large filling defect at the level of C2 is demonstrated.

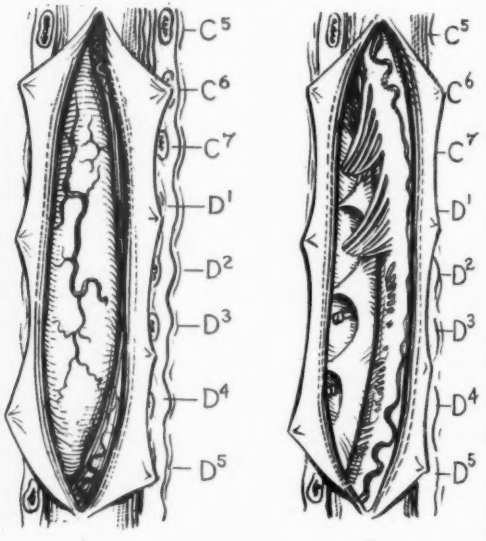


FIG. 4.—Sketch of operative appearances in Case II. (A) tumour exposed and (B) compressed cord after its excision.

Case II.—Miss D., aged 50, had a six-year history of pain in the upper four dorsal dermatomes on the left side, with progressive weakness and numbness in the lower limbs for one year. Examination revealed a severe spastic paraparesis with reduced sensibility below the second dorsal dermatome. Myelography showed a complete obstruction to the upward flow of dye at the fourth thoracic vertebra. At operation a long tumour—a neurinoma—extending from the fifth cervical to the fifth vertebra inclusive was found to be greatly compressing the cord (Fig. 4). The patient made an excellent recovery with a rapid disappearance of abnormal signs.

Although such neoplasms may be of large size their slow growth and their consistency, similar to that of the cord, permit them to accommodate themselves to the available space within the spinal canal. As a result they enlarge in the long axis of the canal and slowly mould the spinal cord perhaps over several segments. When eventually symptoms of a cord lesion do arise they are the result of compression alone and are completely reversible, even when severe, by the removal of the growth.

(ii) *Involvement of the spinal cord by intervertebral disc protrusions.*—I have had the opportunity of operating upon 15 such cases with improvement in all except one fatal case. In 9 the protrusion occurred in the cervical canal and the results of treatment are shown in Table I. Excluding the fatal case which presented with evidence of a complete transverse lesion in the cervical enlargement, the other 8 have been considerably benefited and all have returned to work, apart from the most recently treated patient who had not yet done so when seen three months after his discharge. However all these patients have a residual neurological deficit varying from a mild spasticity of the legs or a unilateral reduction of cutaneous sensibility to a segmental level in the most favourable cases, to spasticity, hyperreflexia, double extensor responses and some sensory disturbance in those with the most severe persistent signs. Why should these space-occupying lesions, small by comparison of the majority of spinal neoplasms, produce a severe disturbance of cord function and a functional deficit which has lasted for periods of fifteen years and which must therefore be considered to be permanent? The answer is, I believe, that an intervertebral disc protrusion not only compresses the spinal cord but also traumatizes it with the production of irreversible

TABLE I.—ANALYSIS OF NINE SURGICALLY-TREATED CASES OF CERVICAL DISC PROTRUSION INVOLVING THE SPINAL CORD

Case and level	Age and sex	Pre-operative state: Motor defect	Pre-operative state: Sensory defect	Post-operative state: Motor defect	Post-operative state: Spast.	Post-operative state: Sensory defect	Post-operative state: Reflexes	Occupation
A. E. C3–4	M. 53	Spastic tetrap.	+	N.	+	N.	N.	Electrician
A. R. C3–4	M. 50	Spastic tetrap.	+	Wk. triceps Rt.	+	+ (Vib.)	Hyper-reflexia P.R. ↑ ↑	(3 months post-op.)
G. T. C4–5	M. 44	Spastic tetrap.	+	N.	+	+ (Vib.)	N.	Clerk
G. R. C4–5	F. 39	Spastic tetrap.	+	Wk. Rt. arm	+	N.	Hyper-reflexia P.R. ↓ ↓	Housewife
L. M. C5–6	M. 44	Spastic hemip.	+	Wk. Lt. hand	+	+ (Rt.)	Hyper-reflexia ↑ ↑	Violinist
G. C. C5–6	M. 39	Spastic tetrap.	+	Wk. Rt. arm	+	N.	Hyper-reflexia P.R. ? ↑ ↑	Gardener
W. B. C5–6	M. 46	Spastic tetrap. (Exc. 1 arm)	+	N.	+	+	Hyper-reflexia P.R. ↑ ↑	Foreman
L. C. C5–6	M. 22	Hemiparesis Lt.	Hemi-anæs. Rt.	N.	—	+ (Rt.)	Lt. S.J. invert	Student
G. R. C7–D1	M. 31	Tetraplegia	+	Died				

changes. Surgery removes the element of compression but cannot undo the effects of past trauma. The protrusion develops more rapidly and is of harder consistency than a neoplasm and therefore does not accommodate itself to the available space. Instead, it produces a severe distortion of the cord—a distortion which is probably the greater because the protrusion occupies but a small part of the length of the spinal canal. The extradural position of a protrusion likewise adds to the risk of cord trauma since during movements of the spine the mass will remain fixed whereas an intradural neoplasm will move with the theca and cord. Anatomical factors, referred to in next paragraph, may contribute to cord injury occasioned by cervical disc protrusions. Injury to the spinal cord occasioned by these factors may account not only for the neurological defect which so commonly persists after excision of a disc protrusion but also for the poor results which have followed operative treatment in a number of reported cases—the addition of even slight operative trauma to that occasioned by the protrusion itself producing very serious results.

In cases of primary cervical spondylosis the osteophytic ridges which cross the floor of the spinal canal usually occupy considerably less space than does a disc protrusion. Even though they be multiple the impression gained at operation is that compression plays but a minor role in the disturbance of cord function in such cases. Here it would seem that trauma has become the more important ætiological agent. Factors responsible for this trauma are the consistency and fixity of the osteophytes, the position of which is rendered the more significant by certain anatomical facts. The anatomical factors now to be considered are peculiar to the cervical region and may account for the fact that myelopathy associated with degenerative vertebral disease is common only when this affects the cervical spine. The first of the two anatomical factors concerns the course of the cervical nerves from the theca through their individual intervertebral foramina (Fig. 5). These nerves,

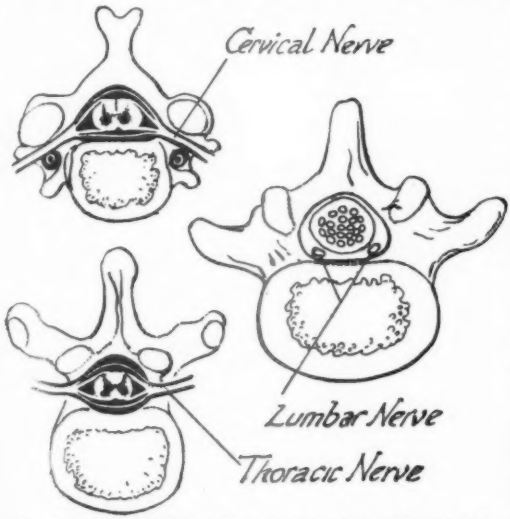
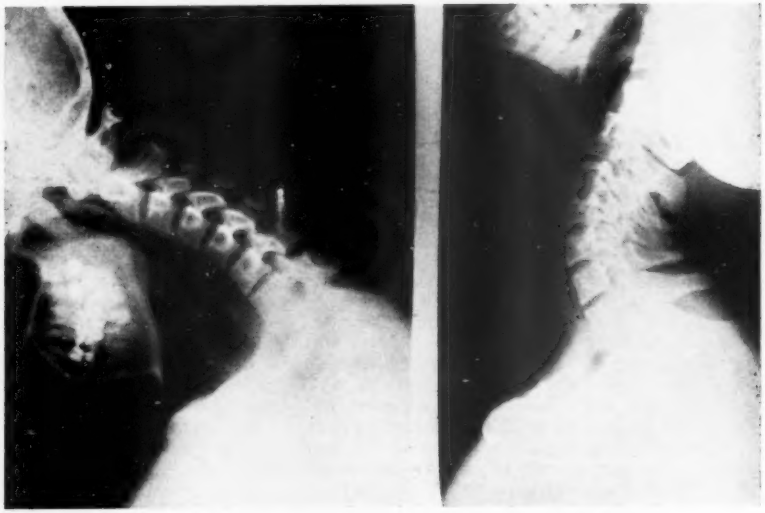


FIG. 5.—The direction of a pair of cervical, thoracic and lumbar spinal nerves is contrasted.

unlike those at other levels, pass with their dural sheaths not only horizontally laterally but also anteriorly, each pair of nerves thus tethering the theca against the posterior surfaces of the vertebral bodies. The large lower cervical posterior nerve roots, which ensheath the cord *en route* from each of these spinal nerves, will exert a similar effect in holding the cord anteriorly in the spinal canal. These tethering effects have been confirmed by noting the increased possibility of posterior displacement of theca and cord following sections of both the spinal nerves and posterior roots in cadavers.

The second anatomical factor concerns the free mobility of the cervical spinal column and the displacements and tensions within the spinal cord to which it gives origin. In Fig. 6A and B are seen X-ray photographs of the cervical spine in full flexion and full extension. In Fig. 7 tracings of these films have been united by superimposing the outlines



A B

FIG. 6 (A and B).—The cervical spine in full flexion and full extension.

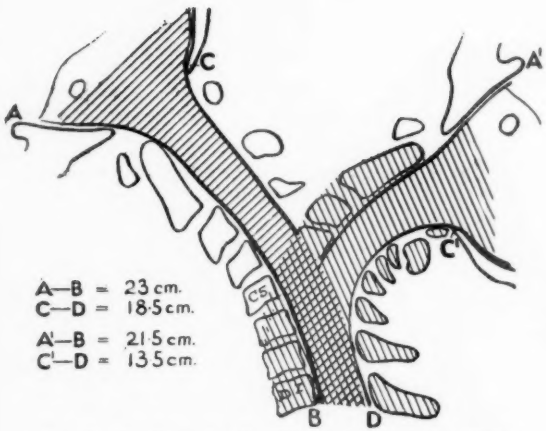


FIG. 7.—Tracings of radiographs in Fig. 6—the outlines of the first thoracic vertebral bodies superimposed.

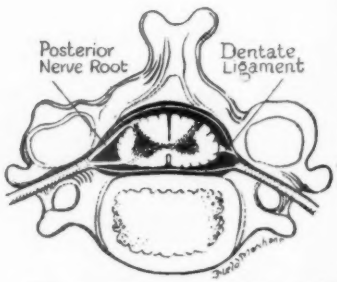
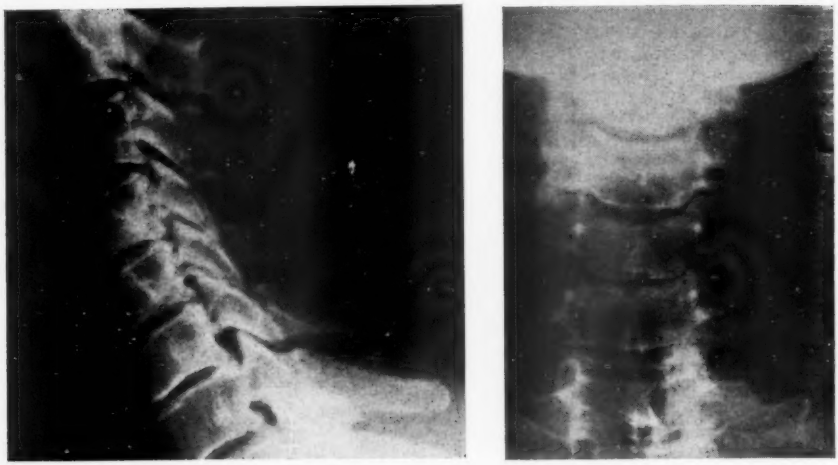


FIG. 8.—The anatomy of the cervical spinal canal in relation to surgical treatment of spondylosis.

of the first dorsal vertebræ. This reveals the change in the direction of the cervical canal amounting to 90 degrees between the position of full flexion and full extension and indicates that stresses occasioned by this change would be maximal opposite the fifth and sixth cervical vertebræ. In the second place it demonstrates the increase in the length of the cervical canal which occurs when the position of the head changes from one of full extension to full flexion; the measurement from the tip of the posterior clinoid process to the lower margin of the posterior surface of the first dorsal vertebra along the anterior wall of the spinal canal increased by 1·5 cm. and that from the posterior margin of the foramen magnum to the lower margin of the first dorsal spine along the posterior wall of the canal by 5 cm. The measurements were made on the spinal films of a young woman, and though greater than would be found in elderly patients they remain of importance in the latter group. In cases of cervical spondylosis the nerve root attachment will hold the spinal cord forward against the anterior osteophytic ridges and during flexion of the neck the apposition of theca and cord to the bony ridges will become more firm. In addition there will be sliding upward and downward movement of the theca and cord across the ridges and stretching of these structures will occur. Recurring minor traumata occasioned by these factors would appear to be an important element in the development of the cord disturbance associated with primary cervical spondylosis. Further, this dysfunction may be regarded as intermediate in severity between the transient but severe disturbance of cord function which may follow hyperflexion of a normal cervical spine (so-called spinal concussion) and the severe and persistent dysfunction which may immediately follow a flexion injury in a patient with spondylosis.

In treatment it is clear that where spinal cord disturbance is occasioned by an intervertebral disc protrusion this should always be excised at the earliest possible time and, with careful surgery, benefit will follow in a high proportion of the cases. Further, the finding of spondylosis largely or entirely localized to one joint should suggest the possibility of an intervertebral disc protrusion at this level and where the age of the patient and the clinical and myelographic findings support this diagnosis exploration is advisable. In cases of what I have called primary spondylosis with diffuse degenerative changes in the spinal joints the problem is more difficult, and the first essential is to establish the diagnosis. When this has been done I believe that treatment should be conservative. The essential aim is to prevent the continuance of recurring trauma to the cervical cord, which is best effected in the first place by bed-rest with cervical traction and later immobilization of the spine in a plastic collar. In addition, exercises and the avoidance of a fatiguing occupation may help the patient to overcome his disability.

Surgery plays only a small part in the treatment of this condition and should be reserved for cases in which conservative measures have failed to prevent progression, when the patient's age justifies an operation of uncertain value, and where both the plain X-ray films and the myelograms suggest the presence of large intraspinal osteophytes. The essential weakness of surgery in the treatment of primary cervical spondylosis lies in the fact that the osteophytic ridges which cross the spinal canal cannot be removed without considerable risk of increasing the patient's disability. The limit of tolerance of further trauma by the already injured cord is small and the manipulations necessary to remove dense bone in the extremely limited space available anterior to the spinal cord is likely to exceed this limit with serious consequences. It is of interest to enquire into the theoretical benefits which surgery might achieve in spite of its essential inadequacy (Fig. 8). In so far as an element of compression is responsible for the neurological disturbance, an adequate laminectomy and incision of the dura, which must be left unsutured at the termination of the operation, will remove the possibility of compression of the cord between the anterior lesion and posterior structures. Further where an intervertebral disc protrusion has occurred from one of the degenerate joints its removal will do much to decompress the cord. In so far as the more important traumatic factor is concerned in producing disturbance of cord function it is clear that symptoms due to structural damage will be permanent and that all that can be hoped for is the reduction of the possibility of further trauma. To the extent that posterior displacement of the spinal cord and its separation from the osteophytic ridges can be facilitated by surgery so will this aim be achieved. While laminectomy itself permits no such displacement there is evidence that a vertical dural incision with lateral transverse extensions will permit a degree of such displacement. The division of several slips of the dentate ligament on each side, as recommended by Kahn (1947), will perhaps increase this displacement. However, as has been stressed, it is the posterior nerve roots which hold the cord against the anterior wall of the spinal canal; the possibility of a wide rhizotomy of the functionally important cervical posterior nerve roots does not exist though the judicious section of one root on each side may be of value. It has been suggested (Taylor, 1951) that injury to the spinal cord in cervical spondylosis is occasioned by the projection into the spinal canal of the ligamenta flava during extension of the neck. Laminectomy will remove the possibility



A B

FIG. 9 (A and B).—Cervical spine of patient with primary spondylosis and severe persistent left brachial pain.

of this occurrence but it should again be pointed out that the chief intraspinal abnormality in cervical spondylosis is anterior to the spinal cord and it is during neck flexion that the relationship of the tense cord to the osteophytic lesions is most intimate. Finally it will be recalled that at times the osteophytes in spondylosis are laterally placed and involve some of the cervical nerves close to and in the intervertebral foramina (Fig. 9A and B). Just as radicular symptoms and signs in the upper limb may be relieved by the excision of lateral disc protrusions, so in this type of spondylosis when the symptoms are severe and persistent decompression of the affected nerves will be of value. This is effected by the excision of the posterior margins of the intervertebral foramina and where possible the osteophytes as well. The patient referred to in Figs. 9 and 10 was considerably benefited by surgery. Where several roots are involved it is likely that the procedure will be followed by at least a temporary increase in the neurological deficit and it should probably be reserved for unilateral cases since excision of the articular processes on both sides is likely to be followed by an unstable column.

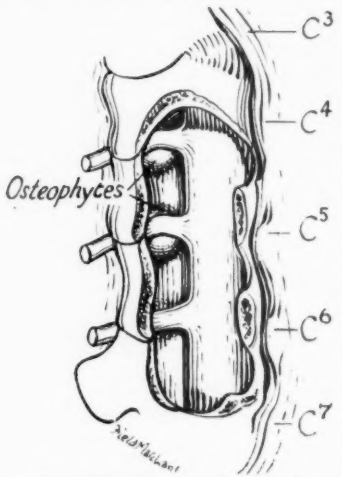


FIG. 10.—Sketch of operative exposure in patient referred to in Fig. 9. The fifth, sixth and seventh cervical nerves have been decompressed by excision of posterior margins of the intervertebral foramina; the osteophytes beneath C7 have been excised, as were the others subsequently.

In conclusion I should explain that because of my opinion that compression plays but a minor role in the production of myelopathy in primary cervical spondylosis and a consequent awareness of the inadequacy of operative treatment in these cases my approach has been extremely conservative, and, I believe, limited to 8 cases. While no one of these was the worse for surgery in only 2 was the benefit unequivocal.

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Section of Endocrinology

President—A. C. CROOKE, M.A., M.D.

[*November* 23, 1955]

DISCUSSION ON THYROTROPHIC HORMONE

Professor Dr. A. Querido (Leiden) and **Miss L. D. F. Lameyer** (Leiden):

Thyrotrophic Hormone Content of Human Sera in Normals and Patients with Thyroid Disease

This study of T.S.H. in body fluid was initiated for three main reasons: It might help (1) in differential diagnosis; (2) in our knowledge of the mechanism of thyroid disease; and (3) in our work on the eye problems associated with thyroid disease.

I shall discuss T.S.H. determination from data obtained in my department mainly by Miss Lameyer (1956) and Dr. A. A. H. Kassenaar.

In our method we use the response to T.S.H. of inhibited mice thyroids, expressed in percentage dose of administered ^{131}I which is accumulated in a definite time (Querido *et* al., 1953). The thyroids are inhibited with iodocasein before the experiment in order to obtain resting glands with low uptake values. Mice are used because they are small, very sensitive to T.S.H. stimulation and easily handled and obtainable. Fig. 1 gives an example of the

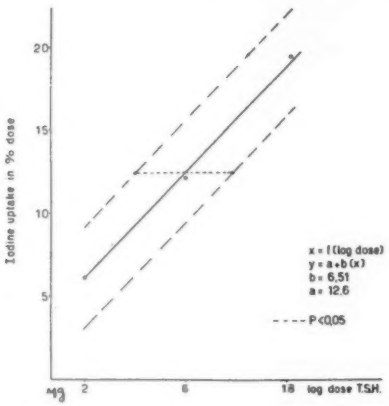

FIG. 1.—Example of dose-response curve.

log. dose/response curve. The error of the technique seems to be very large, and the confidence limits for 95% are ±40–50% dose. The slope of regression line is not constant, and each test therefore requires a new regression line. The slope is, however, independent of season.

The amount of T.S.H. which can be tested with this technique is about 2 μg. U.S.P. standard (equal to about 0·02 J.S.U.) per injection. This is not sensitive enough to assay blood of normal persons, and we therefore had to look for means which enabled concentration of the active principle. From other studies in our laboratory we had indications that T.S.H. in anterior-lobe preparation moves in electrophoresis with speed equal to serum globulins in the ordinary conditions of electrophoresis. In the patient with very high T.S.H. content of the serum this was mainly present in the globulin fraction obtained in paper electrophoresis (Lameyer *et al.*, 1955).

With these facts in mind we started to concentrate and study serum fractions obtained by different procedures. Our purpose was to increase activity, avoiding denaturation. The

first method used was precipitation with 95% ethanol to end concentration of 40% at pH = 5·8 at −5° C. We did in fact, separate the globulins from the albumin fraction and were able to demonstrate the presence of the thyroid gland stimulating activity in the former, while none was present in the albumin fraction.

There were difficulties in dissolving the globulins, and electrophoresis of this fraction made it probable that some denaturation had occurred. We therefore decided to use the more complicated procedure of fractional precipitation described by Cohn *et al.* (1946) for serum. The type of results obtained is shown in Tables I and II. For the different fractions Cohn's

TABLE I.—T.S.H. ACTIVITY IN SERUM PROTEIN FRACTIONS (COHN'S PRECIPITATION AND ELECTROPHORESIS)

Post-operative hypothyroidism (Mrs. W.)

Fraction	mg. protein in 30 c.c. alb.	$\alpha_1\alpha_2$	β	γ	$\%^{131}I$	T.S.H. μg.%*
II + III	78	33	126	447	3·7 ±0·4	—
IV 1	54	39	12	12	3·0 ±0·2	—
IV 4	36	54	51	—	12·0 ±0·9	90–150
V	813	33	33	—	3·7 ±0·3	—
	981	159	222	459		
Serum equal quantity	1,101	183	231	498		

*U.S.P. standard.

TABLE II.—T.S.H. ACTIVITY IN SERUM PROTEIN FRACTIONS (COHN'S PRECIPITATION AND ELECTROPHORESIS)

Post-operative hypothyroidism + local myxœdema (Mr. V.)

Fraction	mg. protein in 30 c.c. alb.	$\alpha_1\alpha_2$	β	γ	$\%^{131}I$	T.S.H. μg.%*
II + III	84	30	147	462	30·1 ±3·2	⟩⟩ 360
IV 1	72	69	15	9	2·1 ±0·2	—
IV 4	24	66	51	—	3·7 ±0·3	—
V	546	27	60	—	1·9 ±0·2	—
	726	192	273	471		
Serum equal quantity	978	216	300	408		

*U.S.P. standard.

nomenclature is used throughout. It appears that all activity in Mrs. W.'s serum seems to be present in fraction IV 4, while in Mr. V. all is found in fractions II and III. Generally the activity is present in fraction IV 4, but it cannot be predicted. All assays of fraction V were negative. It was decided to add the fractions II + III and IV 4 together, and use for assay.

Before reporting the results more comment on the test is required. One question which arises is whether serum thyroxin may be concentrated and influence the result of the test. In experiments where l-thyroxin was added to the material injected, equivalent to amounts of P.B.I. 6·7 μg.% and 20 μg.% in serum, no effect was seen. The negative results obtained with albumin fractions could be due to inhibiting substances. A neutralizing factor, however, could not be demonstrated. The most difficult question was whether the demonstrated thyroid stimulating activity was indeed thyrotrophic hormone. We have added to serum gonadotrophins and ACTH and our results were not altered. We are, however, weak on the evidence for growth hormone. The only point in favour of the absence of a positive effect of growth hormone seems to be that in clinically active acromegaly without thyrotoxicosis we were, on some occasions, unable to demonstrate increased thyroid stimulating activity. Another point in favour is that with serum fractions the same regression was obtained in the test. There is still, however, the possibility that an unknown non-hypophyseal factor is responsible for the test. Being aware of these possibilities, we only propose provisionally to express the results as T.S.H. levels (in U.S.P. provisional standard). The normal values obtained are in the range of 100–200 μg./100 c.c.

The clinical material is divided in a group of thyrotoxics without serious eye signs, a group with serious eye signs, and patients with eye signs without thyrotoxicosis. The diagnosis of thyrotoxicosis depended on clinical signs, on ^{131}I studies and P.B.I. determinations. The classification of eye signs was extremely difficult and arbitrary. Swelling of eyelids, slight proptosis and positive lid retraction were considered not to be serious. For positive eye changes at least one of the following criteria had to be fulfilled: chemosis, paresis of eye movements with double vision and venous congestion of conjunctiva. As our results indicate, an exact classification of the eye signs is unimportant.

Table III shows data on 18 thyrotoxic patients, 9 with and 9 without serious eye signs.

TABLE III.—SERUM T.S.H. IN PATIENTS WITH THYROTOXICOSIS

		T.S.H. >300 μg./100 c.c.	T.S.H. >300 μg./100 c.c.
Without serious eye signs	9	9	—
With serious eye signs ..	9	7	>1,000. One case with frank thyrotoxicosis >1,000 relapsed thyrotoxicosis after thyroidectomy

Only in the latter group there are 2 cases with clearly elevated T.S.H. in the blood. At this point we want to stress that even if hyperthyroidism was accompanied by more T.S.H. than normal, it could not necessarily be demonstrated. We have seen several times in normal individuals a clearcut increase of ^{131}I uptake after a single injection of 10 I.U. of T.S.H. intramuscularly. If this is distributed only to 5 litres of volume, it would mean that an increase in the serum of 20 μg. T.S.H. had to be demonstrated, which evidently is impossible.

We think we have enough support for stating that there is no relation between T.S.H. level in the serum and hyperophthalmopathy. This is again well demonstrated in Figs. 2 and 3.

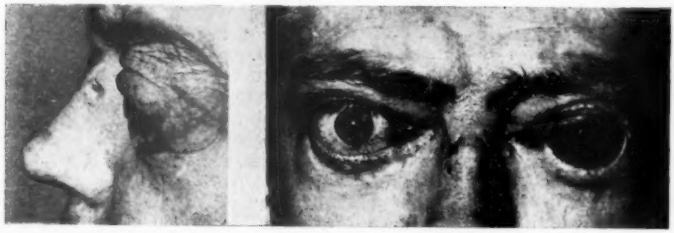

FIG. 2.—Male, aged 42. M.F.L. No. 1379/54. Exophthalmos since July 1952. Thyroidectomy for thyrotoxicosis August 1953. Since then progressive exophthalmos. Hertel L. 33, R. 30 mm. August 1954: B.M.R. −8%; cholesterol 263 mg.%. P.B.I. 5.6 γ/100 c.c. T.S.H. 2×absent in serum.

FIG. 3.—Male, aged 25. C.V. No. 6194/50. 1949: Thyroidectomy for thyrotoxicosis. Local myxœdema some weeks later. 1953: B.M.R. −21%; cholesterol 390 mg.%. P.B.I. 2·1 γ/100 c.c. T.S.H. >12 mg./100 c.c. serum. Slight protrusion of eyes.

Mr. L. had the most active form of progressive exophthalmos ever seen in our department. The eyes actually proptosed further under our observation. He was euthyroid, and repeatedly no raised T.S.H. level could be demonstrated. Mr. V. had the highest values for T.S.H. (more than 12,000 μg. U.S.P. per 100 c.c.) having post-operative myxœdema, slight

proptosis and pretibial myxœdema. The contrast between these 2 patients seems to strengthen our argument.

It seems clear that there is no relation between exophthalmos and serum T.S.H. level. This, however, does not necessarily mean that T.S.H. is unrelated to eye signs. Theoretically a level in the serum may be high both with low or high production.

I shall refer briefly to the application of the T.S.H. assay in blood for differential diagnosis of primary and secondary myxœdema. As in our test we do not always find T.S.H. even in normal serum, we feel that only the finding of raised T.S.H. levels is significant and supports the diagnosis of primary myxœdema.

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Dr. I. C. Gilliland:

Clinical Experience with T.S.H. Estimation

The method we used (Gilliland and Strudwick, 1953), like that of Professor Querido's, depends upon the use of an animal pretreated with thyroxin. Day-old chicks are injected with 8 μg. of l–thyroxin daily for three days. We load them with 20 μc ^{131}I before this, so that at the end of three days the chicks have inactive thyroids containing ^{131}I-labelled hormone. This labelled hormone can still be discharged by the administration of T.S.H. and the percentage of ^{131}I discharged measures the T.S.H. given. We prefer to use discharge rather than uptake as we feel it is one of the most specific actions of T.S.H.

We use an *in vivo* counting device so that we can measure the ^{131}I content of the thyroids of these prepared chicks before and after administration of T.S.H. The difference of the counts before and after is expressed as a percentage discharged. The discharge of ^{131}I bears a linear relationship to the log. dose of T.S.H. over the range used so the method can be adapted to a "4-point assay". We use two "points" on the line of known T.S.H. and compare this with two "points" of the unknown serum. It has the advantage of enabling a computation to be made of the validity of the assay, and an estimate of the limits of confidence.

We have used serum throughout, but would agree with Professor Querido that some sort of concentration method would be useful, especially in the normals in whom large amounts of serum are necessary for the estimation.

RESULTS

Our results have been published elsewhere in detail (Gilliland and Strudwick, 1956). We were unable to obtain any response in 3 patients with Simmonds' disease, whilst 8 patients with spontaneous myxœdema showed a high serum concentration of T.S.H. Two patients with recently induced myxœdema and 2 cretins showed an even greater concentration of T.S.H. Two patients with long-standing severe myxœdema showed no response, but one of these, tested again after partial substitution therapy, showed the same high level of T.S.H. as the other patients with spontaneous myxœdema.

We investigated a further 3 groups of patients: (*a*) Thyrotoxicosis with severe eye signs (9), (*b*) thyrotoxicosis without severe eye signs (5), and (*c*) severe eye signs without thyrotoxicosis (3).

Thyrotoxicosis with severe eye signs was associated with a raised T.S.H. level in the serum comparable with spontaneous myxœdema. Of the 5 patients with thyrotoxicosis without severe eye signs, 3 gave no response and 2 showed a measurable level of T.S.H. somewhat lower than those with severe eye signs. The 3 patients with severe exophthalmos who were not thyrotoxic showed levels of T.S.H. which did not differ from normals.

DISCUSSION

The presence of high levels of serum T.S.H. in most patients with spontaneous myxœdema, in induced myxœdema and in cretinism, all unassociated with exophthalmos make it unlikely that T.S.H. alone is the cause of this exophthalmos: some other factor must be involved.

One of the 2 cases of profound and long-standing myxœdema on retesting showed that her pituitary had recovered its ability to secrete T.S.H. This finding has already been

recorded by Starr *et al.* (1939). We also estimated follicle stimulating hormone in this case (Fig. 1, Profound Myxœdema). F.S.H. was absent in her profoundly myxœdematous state but returned at the same time as the T.S.H. which would confirm that the pituitary is itself depressed in severe myxœdema. The finding of even higher levels of T.S.H. in recently induced myxœdema, also recorded by Rawson and Starr (1938), would lend support to this conception.

The one cretin who was retested when on complete substitution therapy showed no T.S.H. at this point, but his F.S.H. which was originally absent was then at a high level (Fig. 1, Cretin).

The high levels of T.S.H. in thyrotoxicosis with severe exophthalmos would suggest that this is associated with pituitary activity, whilst the different findings in those without severe exophthalmos might suggest a different type of thyrotoxicosis (De Robertis, 1948) or a different stage of the disease. A comparison between the T.S.H. levels and protein-bound iodine levels in some of these cases where the measurement was made simultaneously would tend to support this (Fig. 2). The three cases with severe exophthalmos may be considered

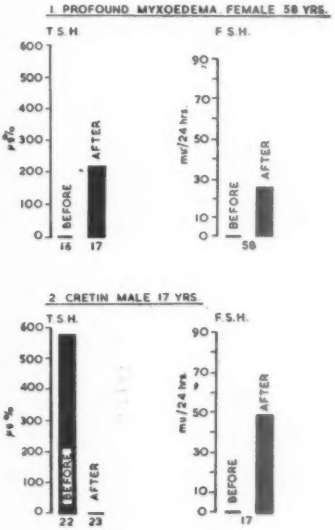

FIG. 1.—Pituitary response to treatment.

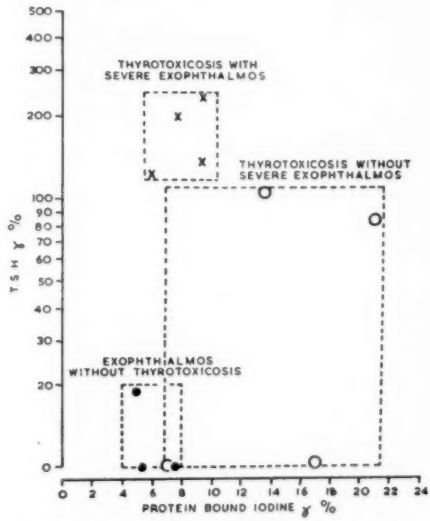

FIG. 2.—Comparison of P.B.I. and T.S.H. in exophthalmos.

as Graves' disease in which only the eyes are affected. On this assumption we have shown that severe exophthalmos can exist without a raised T.S.H. level just as a raised T.S.H. level can exist without exophthalmos. It remains possible that these 3 cases are examples of some other disorder.

Our findings, like those of Professor Querido, show that there is no direct correlation between the level of T.S.H. circulating and the presence of exopthalmos. The results would be best explained by the claim of Dobyns and Steelman (1953) and Dobyns and Wilson (1954) that the pituitary produces a separate factor capable of causing exophthalmos.

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Section of Anæsthetics

President—T. Cecil Gray, M.D., F.F.A.R.C.S., D.A.

[*December* 2, 1955]

DISCUSSION ON CARBON DIOXIDE ACCUMULATIONS IN ANÆSTHETIC CIRCUITS

Dr. A. Bracken (The Research and Development Centre of The British Oxygen Company Limited):

Introduction

This lecture summarizes work carried out mainly at the Research and Development Centre of the British Oxygen Company Limited.

We began our investigations about five years ago in answer to a simple question from our Medical Division: "How can carbon dioxide absorption be improved to the benefit of anæsthetists and patients?" We believe we have answered the immediate question by the introduction of an improved soda lime, but consideration of the general problem is still continuing.

Put in its simplest form the removal of CO_2 from an anæsthetic circuit consists of the reduction of the CO_2 concentration from about 4% v/v (the concentration in the gas stream leaving the patient's mouth) to approximately zero (the concentration in the atmosphere is 0·03% v/v).

Our experience in the industrial field was only of indirect use to us as the particular problem arising in anæsthesia offers special difficulties which limit the choice of absorbent.

The Absorbent

(*a*) *Alternatives to Soda Lime*

As soda lime for carbon dioxide absorption has several well-known disadvantages we investigated some of the reagents used in industry and several others, but nothing markedly better than soda lime was found.

We tried cold water (but found that the flow rate required would be too great) and aqueous solutions of various substances, some of which are shown in Table I. One general objection

Table I.—Carbon Dioxide Absorption by Aqueous Solutions of Bases

Gas mixture, 4% carbon dioxide in air. Gas flow rate, 500 c.c. per minute. Volume of solution used, 100 c.c.

Absorbent used	Time, min.	Issuing gas % CO_2	Absorbent used	Time, min.	Issuing gas % CO_2
10% sodium carbonate ..	1	3·3	10% triethylene tetramine	85	0·3
	109	3·6		124	0·9
10% potassium carbonate	1	2·7		143	2·2
	120	3·1	10% diethylene triamine..	108	0·1
10% suspension of calcium hydroxide	1	1·4		134	0·5
	30	1·2		158	1·6
10% sodium hydroxide ..	82	0·2	10% 4 : 4′ :-dipiperidyl ..	48	0·3
	95	0·7		70	2·0
10% triethanolamine ..	1	1·7	A column of soda lime occupying the same volume as the aqueous solutions used above ..	127	0·2
	57	2·4			

to the use of aqueous solutions is that they would almost certainly lead to increased resistance in the circuit, although they would have several advantages, such as the absence of heating effects, the possibility of regeneration of the absorbent, and the admissibility of Trilene to closed circuits.

(*b*) *Soda Lime*

(i) *Composition.*—We were thus driven back to soda lime and carried out numerous analyses in the early stages of our work; a typical result is shown in Table II.

TABLE II.—AVERAGE COMPOSITION OF SODA LIME %

Caustic alkali (as NaOH) ..	4·0	Calcium carbonate	9·0
Water	15·0	Iron and alumina	1·0
Calcium hydroxide	70·0	Acid insoluble matter.. ..	1·0

Of these substances calcium carbonate is an end-product and the last two items are binders or impurities. The three items listed in the first column are the vital constituents so that soda lime may be regarded as a 20% aqueous solution of sodium hydroxide dispersed on calcium hydroxide.

(ii) *Mechanism of carbon dioxide absorption.*—As the absorption of each molecule of CO_2 results in the liberation of one molecule of water, soda lime is therefore wet with respect to the gas stream passing through it.

(iii) *Water content.*—The water content is clearly most important, and soda lime must not be allowed to become dry. For further discussion *see* Bracken and Sanderson (1955*a*).

(iv) *Indication of approaching exhaustion of soda lime.*—It would be very useful to provide unmistakable evidence of the approaching exhaustion of soda lime. Attempts have been made to popularize "indicator soda lime" in which a dye is included, a colour change indicating exhaustion of the soda lime, but we are not altogether satisfied with this. A rough guide is to correlate the amount of heating in the canister with the efficiency with which carbon dioxide is being absorbed. As will be seen from Fig. 1, even when the

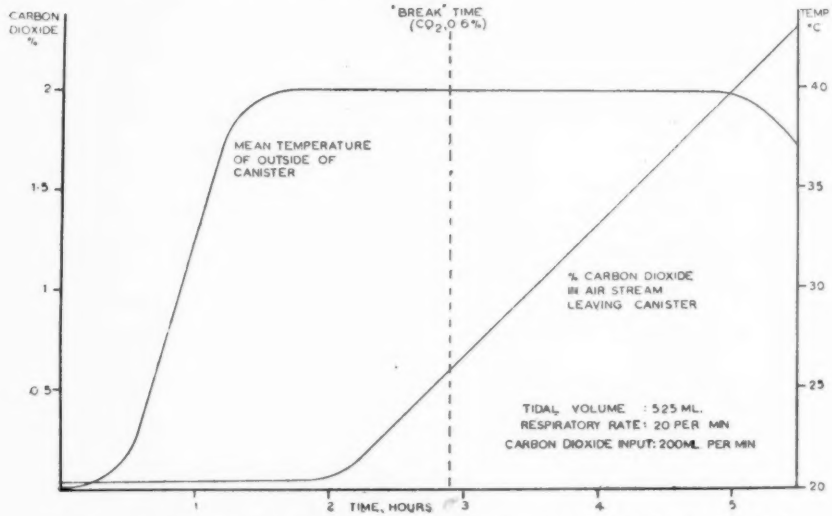

FIG. 1.—Carbon dioxide absorption in Waters canister. Comparison of temperature of canister and efficiency of absorption.

temperature of the canister is 40° C., the concentration of CO_2 issuing from it can be as high as 2%. It is clear that a hot canister does not necessarily indicate efficient absorption of CO_2. The only reliable method is to analyse the gas stream emerging from the canister or apparatus. We have recently devised a neat little apparatus for this purpose.

[A small colorimetric carbon dioxide analyser was then demonstrated.]

This can be used at present only on apparatus where unidirectional valves are provided, but we are endeavouring to extend its usefulness.

(v) *Testing soda lime.*—Several tests of soda lime are given in the British Pharmacopœia (G.M.C., 1953), but in order to test its efficiency under conditions which approximate to

those found in practice, we devised a circle test using a standard 1 lb. canister (Fig. 2). Typical results obtained with this apparatus are shown in Fig. 3.

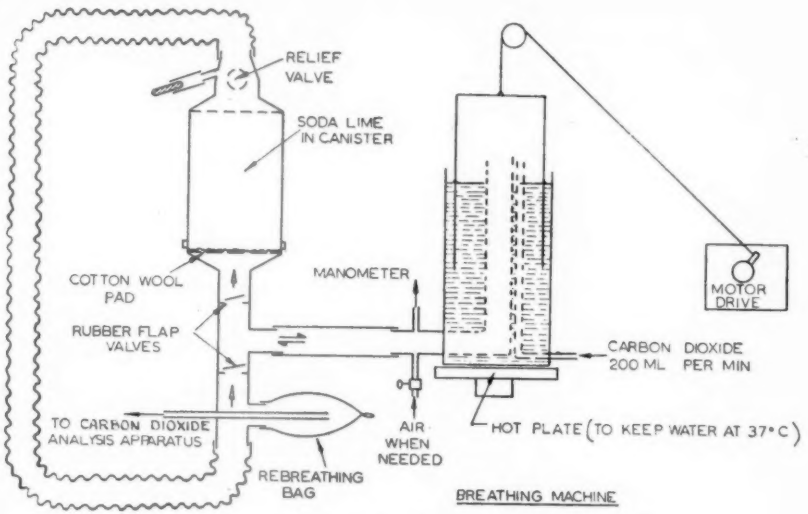

FIG. 2.—Apparatus for circle carbon dioxide absorption test.

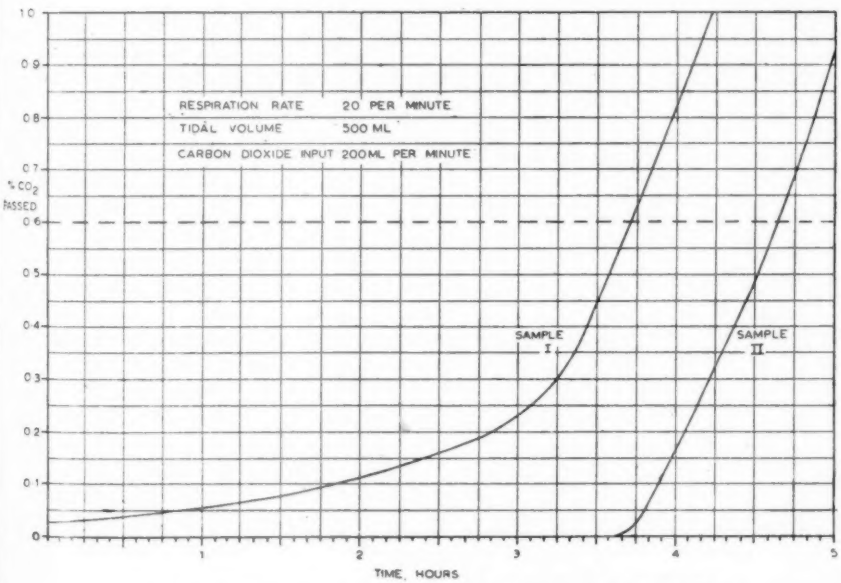

FIG. 3.—Comparative standard circle tests on two samples of soda lime.

It will be seen that the better sample (sample 2) returns an immeasurably small quantity of CO_2 to the system for over three and a half hours using a breathing machine with the respiration conditions indicated, whereas the inferior sample returns some carbon dioxide even at the beginning of the test.

Apparatus and Circuits

Although our work began as an endeavour to improve carbon dioxide absorption it soon became clear that another problem was involved, namely the most satisfactory elimination of CO_2 from the circuit itself.

(a) Canister and Channelling

We repeated some of Adriani's work on channelling using his test with similar results (Adriani, 1946). Efficient packing of the soda lime is especially important with the Waters absorber, because this is normally used with the canister in a horizontal position and it is then very easy for a channel to form along the top of the soda lime.

(b) Infra-red Analyser

The analysis of the gas mixture inhaled and exhaled by the anæsthetized patient is one of the outstanding problems of anæsthesia, because the analyst must deal with a rapidly moving gas stream of constantly changing composition. An infra-red analyser was available to us and in view of the success of earlier workers (referred to in Bracken and Sanderson, 1955*b*) was employed for our purpose.

[The principles on which the infra-red analyser operates were mentioned (Bracken and Sanderson 1955*b*) (Fig. 2).]

The analyser has a very short response time, about 0·2 second, and an accuracy of about $\pm 0{\cdot}05\%$ in the range we have so far covered, namely 0–7% CO_2. It was arranged so that N_2O did not interfere with the readings.

A flow rate of about 1·5 litres per minute is required through the analysis cell. This means that when the apparatus is used on a breathing circuit, whether in conjunction with a breathing machine or with a human subject, arrangements must be made to return the sample to the system. There is no difficulty here with a breathing machine but when anæsthetized patients were used it was necessary to devise a system of double intubation. We are glad to acknowledge here the guidance we received from Dr. S. de Clive Lowe, St. Luke's Hospital, Guildford, who first used our analyser under operating theatre conditions and solved this problem of double intubation for us.

(c) Anæsthetic Circuits

Tests were carried out on the four circuits shown diagrammatically in Fig. 4, types (*a*), (*b*) and (*c*) being examined initially in the laboratory, employing a standard respiration rate of 20 per minute, with a tidal volume of 500 c.c. The carbon dioxide input was 200 c.c. per minute (equivalent to an "inhaled" CO_2 concentration of 4·5%).

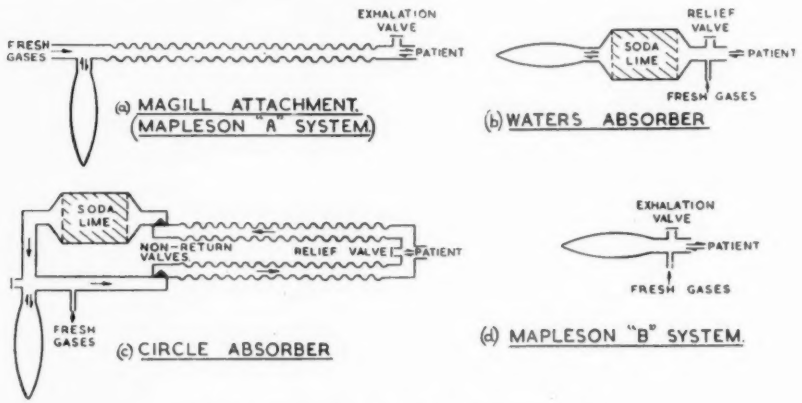

FIG. 4.—Anæsthetic circuits tested (diagrammatic).

(i) *Magill attachment.*—This semi-closed circuit was first investigated by Professor Pask and his co-workers (Molyneux and Pask, 1951), who did not, however, use the name "Magill", and later by Dr. Woolmer (Woolmer and Lind, 1954) who used the name, and at the same time by Dr. Mapleson (1954), who referred to it as his "A" system. We have found the nomenclature used by Dr. Mapleson to be particularly useful in dealing with other semi-closed circuits.

Our breathing machine tests on the Magill attachment gave the results shown in Table III.

TABLE III.—MAGILL ATTACHMENT: VARIATION OF INHALED CARBON DIOXIDE CONCENTRATION WITH GAS INPUT USING BREATHING MACHINE

Standard respiration conditions as in para. *c* of text

Input flow, litres per minute ..	2	4	6	8	10
CO_2 inhaled, %	2·7	1·35	0·7	0·3	0·1

TABLE IV.—UNIDIRECTIONAL CIRCLE ABSORBER USED AS SEMI-CLOSED CIRCUIT WITHOUT SODA LIME: VARIATION OF INHALED CARBON DIOXIDE CONCENTRATION WITH GAS INPUT USING BREATHING MACHINE

Standard respiration conditions as in para. *c* of text

Input flow, litres per minute ..	2	4	6	8	10
CO_2 inhaled, %, ether full "on"	4·15	1·6	0·75	0·3	0·15
CO_2 inhaled, %, ether "off" ..	3·9	1·4	0·7	0·25	0·1

(ii) *The Waters Absorber.*—The inhaled carbon dioxide concentration obtained from a Waters absorber will depend on the amount re-inhaled from the deadspace and therefore, in a closed system, on the volume of this deadspace (which will include the volume occupied by exhausted soda lime). In repeat experiments with the breathing machine operating under our standard conditions (*see* para. *c*), the "inhaled" CO_2 concentration was effectively zero for three and a half hours, reached 0·15% after four hours, and then rose steadily owing to exhaustion of the soda lime reaching 0·6% in four and three-quarter hours and 1·0% in five hours. The effects of varying breathing rates and other conditions have also been examined with results qualitatively similar to those obtained by Adriani (Adriani, 1946). We did not find any useful relationship between the "inhaled" CO_2 concentration and that in the rebreathing bag. The latter concentration always increased some time before there was any increase in the former. This was because further absorption took place on return through the soda lime (Adriani, 1946).

(iii) *Circle type absorber.*—In this type of absorber the gas stream passes only once through the soda lime. CO_2 elimination from anæsthetic circuits of this type is, however, better than that from circuits based on the to-and-fro system, because of the much smaller deadspace.

In tests carried out with the breathing machine, used under our standard conditions (*see* para. *c*), the "inhaled" CO_2 concentration remained between 0·1% and 0·2% for four and three-quarter hours, and then rose sharply owing to exhaustion of the soda lime. We also carried out tests on a circle absorber used as a semi-closed system with the soda lime out of circuit. The results (Bracken and Sanderson, 1955*b*) are shown in Table IV.

(iv) *Comparative tests with anæsthetized patients.*—Tests with anæsthetized patients were first carried out at St. Luke's Hospital, Guildford, and later at Queen Victoria Hospital, East Grinstead. Later work at Westminster Hospital, in which exhaled samples were analysed, in conjunction with Dr. C. F. Scurr, and at Guy's Hospital with Dr. J. M. Hall and Dr. R. J. Vale, is incomplete and therefore not yet ready for public mention. Thanks to the kindness of Dr. de Clive Lowe and Dr. Russell Davies, I can, however, refer briefly, in advance of full publication, to the results obtained at Guildford and East Grinstead respectively.

TABLE V.—COMPARISON OF INHALED CARBON DIOXIDE CONCENTRATIONS OBTAINED WITH ANÆSTHETIZED PATIENTS AT ST. LUKE'S HOSPITAL, GUILDFORD

Apparatus	No. of readings	Mean inhaled CO_2, %
Magill attachment ..	128	0·43
Mapleson "B"	142	1·49
Waters absorber: semi-closed	75	0·33
Unidirectional circle absorber: semi-closed	138	0·07
Waters absorber: closed circuit	13	1·10
Unidirectional circle absorber: closed circuit	16	0·29

TABLE VI.—COMPARISON OF INHALED CARBON DIOXIDE CONCENTRATIONS OBTAINED WITH ANÆSTHETIZED PATIENTS AT QUEEN VICTORIA HOSPITAL, EAST GRINSTEAD

Circuit employed	No. of readings	Mean inhaled CO_2, %
Magill attachment .. (Mapleson "A")	107	0·29
Mapleson "B"	109	1·75
Ayre's "T"-piece .. (Mapleson "E")	131	1·59

The results of tests at St. Luke's Hospital are best summarized in Table V, from which it will be seen that the Mapleson "B" system (d, of Fig. 4) was examined as well as the other

circuits tested in the laboratory. In all cases a constant gas flow of 7 litres per minute was used (2 l. per minute of O_2 plus 5 l. per minute of N_2O). The patients were intubated and N_2O was the only inhalation anæsthetic used.

The results of the tests carried out at the Queen Victoria Hospital, East Grinstead, are given in Table VI where it will be seen that T-piece anæsthesia was also examined. As before, a constant gas flow of 7 litres per minute was used, the patients were intubated and N_2O was the only inhalation anæsthetic used.

In both these series of tests a large number of cases was investigated and the figures given are the mean values of many determinations. Owing to the satisfactory nature of the technique developed with our anæsthetist collaborators, it was possible to apply several circuits to the same patient during the more prolonged operations. Towards the end of the experiments we came to use the Magill attachment as our criterion so that during the shorter cases we would use the Magill attachment and then one other anæsthetic circuit.

Doubling of the input flow rates in the cases of Mapleson systems "B" and "E" appeared to produce readings comparable with those obtained with the Magill attachment at 7 litres per minute, but the number of readings obtained was not large enough to be absolutely conclusive. We have no reason, however, to doubt the validity of the conclusions reached on theoretical grounds by Dr. Mapleson (1954).

Conclusions

As a result of this work we have been able to draw the following conclusions. Carbon dioxide rebreathing is best prevented by using a unidirectional circle type absorber, with soda lime as absorbent in a semi-closed system and with a total gas flow of not less than 7 l. per minute, venting excess gases as near to the patient's lips as possible. Under these conditions of gas flow the Waters absorber (semi-closed) and the Magill attachment are also satisfactory. The unidirectional circle-type absorber is better in closed circuit than the Waters absorber, mainly because of rebreathing from the deadspace in the latter. Both the Mapleson "B" system and the Mapleson "E" system (Ayre's T-piece) return high CO_2 concentrations to the patient when used with fresh gas flow rates of about 7 l. per minute. Doubling the normal gas flow rate appears to be one method of reducing CO_2 rebreathing in such systems.

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Dr. S. G. de Clive Lowe: *Carbon Dioxide in Anæsthesia*

This investigation was started because of the adverse comments of our surgical colleagues, following the introduction of a new and somewhat revolutionary method of anæsthesia, and also because of certain anxieties in our own minds as to whether some post-operative symptoms were not, in fact, due to accumulation of CO_2. Dr. J. North and I carried out the investigation, under the guidance of Dr. A. Bracken, and his colleague Mr. D. M. Sanderson of the British Oxygen Company at St. Luke's Hospital, Guildford, early in the year.

The method used was as follows: Unselected patients were all intubated with a cuffed endotracheal tube connected to the catheter mount by a Nosworthy connector. The sample was drawn from a T-piece on a small adaptor, made to fit between the two halves of the Nosworthy connector, and returned to a point just above the carina by means of a small gum elastic catheter (No. 7 F), passed previous to the endotracheal tube, as shown in Figs. 5 and 6. The reason for this procedure was that when the apparatus is used on a closed breathing circuit, the sample must obviously be returned to the system on the pulmonary side of the sampling point, and not too close to the latter or interference with the system will occur which may render the readings invalid. It was found by experiment that this arrangement was satisfactory and that a number of respirations could be observed in a single sampling operation without appreciably disturbing the system.

In most cases, sufficient seal round the catheter was obtained by inflating the cuff of the endotracheal tube, though in a few cases the insertion of a throat pack was necessary.

While the analyser was in use, only nitrous oxide and oxygen were delivered to the patient for inhalation, since trichlorethylene, chloroform, diethyl ether and cyclopropane would cause interference with the analyses, and the two latter might also cause an explosion. All other drugs were given intravenously.

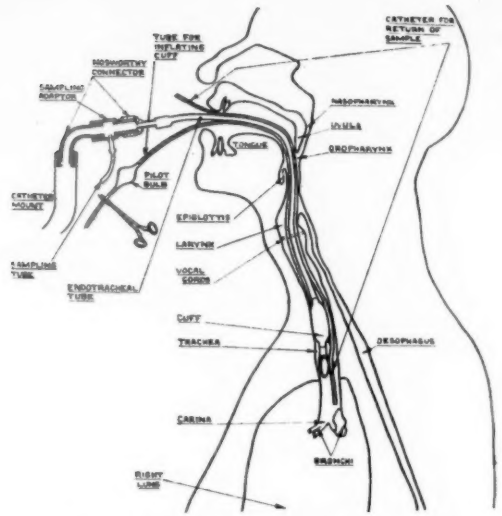

FIG. 5.—Section of patient, showing intubation.

Anæsthetic circuits.—It was now felt that a satisfactory apparatus and method were available for checking CO_2 accumulation and elimination in some commonly-used circuits. The great advantage of the method was the number of readings which could be taken in a short time. Tests were now carried out on the following circuits:

(1) Mapleson "B" System.
(2) Magill Attachment.
(3) Waters Absorber.
(4) Unidirectional Circle Absorber.
(5) To-and-fro cum Circle Absorber (Coxeter-Mushin).

Technique.—50 cases were examined. In all cases induction was with thiopentone sodium followed by a relaxant, usually succinyldicholine chloride for intubation. In these cases a combined succinyldicholine/lignocaine drip was set up in the theatre, narcosis being maintained with N_2O and O_2. Occasionally *d*-tubocurarine, or gallamine triethiodide (Flaxedil) were used in place of succinyldicholine, in which case the lignocaine drip was omitted and pethidine used. Chlorpromazine was also used on occasion. The use of a succinylcholine drip was very convenient, since the patient's tidal volume could be reversibly controlled by adjustment of the drip rate owing to the drug's rapid action and elimination.

Throughout the tests, the gaseous inflow rate was kept at a total of 7 l. per minute (2 l./min. O_2, 5l./min. N_2O). Fresh soda-lime was used throughout, care being taken to ensure that all absorbers were completely filled. Where it was not possible to use all the circuits on a given patient, attention was concentrated on the comparison between the Mapleson "B" circuit and Magill attachment. These principal results are shown in Tables I – III.

During the tests on the semiclosed Circle Absorber, it was found that less CO_2 was reinhaled using the relief valve on the facepiece, than by using that in the lead to the rebreathing bag.

A separate test on the Magill attachment showed that no appreciable concentration of carbon dioxide reached the rebreathing bag while the total inflow remained at 7 l./min., even with a moderately large tidal volume.

It was found that the setting of the relief valve made very little difference, since the variation in volume of the full rebreathing bag is very small over this small pressure range.

With the Mapleson "B" circuit, occasional complete emptying of the bag was of little advantage, as the inhaled concentration had returned to former level after two respirations. In general, slightly lower values were obtained when respiration was assisted, but this might well have been due to the increased tidal volume obtained.

FIG. 6.—Showing connections to patient.

A constant tidal volume was aimed at, and controlled by adjustment of the drip rate of succinylcholine.

There was considerable spread of the results due to variations between the patients, and to variations in the same patient of factors such as tidal volume, respiratory rate, assistance to respiration, metabolic rate, presence of emphysema, and angle of tilt of the table. The results were examined statistically and were found to be sound.

On a number of occasions during these tests, when the concentration of inhaled CO_2 was high, complaints were made by the surgeon of considerable bleeding in the form of capillary oozing, which ceased when the concentration was reduced. The surgeon was not aware of the readings obtained, or of the method of administration in use at the time.

A second series of 10 patients was examined using the To-and-Fro cum Circle absorber in three ways:

(1) As a semiclosed circuit, soda lime on.

(2) As a semiclosed circuit, soda lime off.

(3) As a closed circuit.

The results are compared with the corresponding ones from the first series in Table III (Dr. Bracken).

TABLE I.—SEMICLOSED CIRCUITS.

Comparison of Inhaled CO_2 Concentrations

Apparatus	No. of readings	Mean % CO_2
Mapleson "B" circuit	142	1·49
Magill attachment ..	128	0·43
Waters absorber ..	75	0·33
Circle absorber ..	138	0·07

TABLE II.—MISCELLANEOUS CIRCUITS

Comparison of Inhaled CO_2 Concentrations

Apparatus	No. of readings	Mean % CO_2
Waters absorber: closed circuit	13	1·10
Circle absorber: closed circuit	16	0·29
Circle absorber: semiclosed without soda lime	6	0·78

TABLE III.—TO-AND-FRO (COXETER-MUSHIN) AND UNIDIRECTIONAL CIRCLE ABSORBERS

Comparison of Inhaled CO_2 Concentrations

	Coxeter-Mushin		Circle absorber	
Method of use	No. of readings	Mean % CO_2	No. of readings	Mean % CO_2
Semiclosed: soda lime on	48	0·91	138	0·07
Semiclosed: soda lime off	7	1·40	6	0·78
Closed circuit	49	2·59	16	0·29

Two such machines were used during these tests, and there was no appreciable difference between them.

It was demonstrated in separate tests that with the ether vaporizer in circuit, the CO_2 concentration was further increased.

It would appear from these results, that the most efficient way of reducing CO_2 concentration in semiclosed circuits is to use a unidirectional circle absorber with the soda lime in circuit. Next in order comes the Waters absorber closely followed by the Magill attachment. The To-and-Fro/Circle comes next, and last and worst of all is the Mapleson "B" Circuit. A 7 l.minute volume is assumed in all these cases. Mapleson's reasoning on the Magill attachment is confirmed by our failure to detect CO_2 at the bag mount.

Closing the circuit automatically increased the inhaled concentration, since gases in the dead space near the lips can no longer emerge from the relief valve. This also explains the lower efficiency of the circle system using the valve in the bag lead. On closed circuit the unidirectional circle absorber remained the most efficient.

It will be seen that the unidirectional circle absorber, under all conditions has a markedly greater absorptive efficiency than the To-and-Fro/Circle type. The latter is particularly bad in closed circuit.

The Mapleson "B" circuit is normally only used for short periods so that in this case the blood plasma and tissue carbon dioxide tensions have not time to rise to dangerous levels.

It is certainly possible that both these latter methods have been responsible for considerable serious post-operative trouble, if not fatalities, in the hands of the unwary.

Recognition of carbon dioxide accumulation in a patient, before it reaches a high level, is extremely difficult, particularly in anæsthesia where depressants are used. This was fully confirmed by experiences during these tests.

These facts apply particularly to the Mapleson "B" system, and the To-and-Fro/Circle absorber, so much so that we have now discontinued the use of both, but have, by a simple modification converted the latter to a Circle type.

Dr. Ronald Woolmer: *Carbon Dioxide Concentrations in Anæsthesia.*

Throughout the animal kingdom the tension of carbon dioxide in the blood is regulated with great nicety, and a number of mechanisms are concerned with its control.

The pathological processes which may cause departures from normal levels are well known, but it is not always realized how important anæsthesia is in this respect.

The normal healthy subject breathes in a mixture containing virtually no CO_2. His ventilation is readily altered from moment to moment at the behest of an alert respiratory centre, and his kidneys are effective in countering maladjustments of acid-base balance. In the anæsthetized patient none of these things may be true, and serious deviations of CO_2 homeostasis may result.

Excess CO_2 can produce a train of adverse effects throughout the body. The converse—usually a result of imposed hyperventilation—causes equally complex derangements. These include a serious diminution of cerebral blood flow, a shift of the oxygen dissociation curve to the left, which impedes the uptake of oxygen by the tissues, and peripheral vasoconstriction with stagnant anoxia.

Serious departures from the normal level are easily produced during anæsthesia. The frail, elderly patient subjected to "controlled respiration", particularly with a closed circuit, is very easily forced into acute respiratory alkalosis. A patient with a high metabolic rate, on the other hand, can equally easily be made acidotic by faulty methods of anæsthesia.

What we need is a ready means of indicating departures from the normal CO_2 values: a method as simple to use as the sphygmomanometer. It would give very much more valuable information than that instrument.

Unfortunately the problems of instrumentation, though simple to formulate, are difficult to solve. Ideally, we want an instrument which will give a continuous indication of the partial pressure of CO_2 in the arterial blood. It should have a rapid response, it should be accurate to within 2 mm.Hg and it should be easy to read, easy to work, small, non-explosive and cheap. Of course, we are nowhere near it. Even single direct estimations of the arterial CO_2 pressure are difficult and time-consuming. Continuous ones are impossible. So we have to attempt an indirect estimate. In most cases it is a legitimate assumption that "alveolar air" has the same CO_2 pressure as arterial blood. Alveolar air, however, is easy to define but difficult to obtain, even in the laboratory, to say nothing of the operating room.

Air from the depths of the lungs, which should be "alveolar", comes during expiration into the trachea and pharynx, where it is available for sampling. Here we have the difficulty that if the sample is a small one it may have come from alveoli which were well perfused but poorly ventilated, or well ventilated but poorly perfused, and hence is unrepresentative. If

the sample is a large one its collection often creates abnormal conditions. "Spot samples", therefore, are likely to be misleading, and continuous analysis is required. This obviously rules out the more conventional methods of gas analysis, such as Haldane's or Scholander's, and drives us to look for methods which can be made continuous.

Up to the present, four such methods have been investigated: infra-red analysis, differential absorption, mass spectrometry and photometry with an indicator.

Dr. Bracken has already mentioned infra-red analysis. The principle of differential absorption has been embodied in the Rowling-Ringrose-Harbord indicator (Ringrose *et al.*, 1950) and other instruments. Mass spectrometry has been used in anæsthesia (Miller *et al.*, 1950), but it is a complicated method. The photometric method is the one which I have used.

Methods of continuous sampling may be divided into four groups: (*a*) the whole tidal volume may pass through an analyser inserted in the airway close to the facepiece. This will show inspiratory and expiratory levels of CO_2. (*b*) By the interposition of appropriate valves, the whole of one phase of respiration may be passed through the analyser. (*c*) A fraction of the whole tidal volume may be analysed. (*d*) A fraction of one phase may be analysed. It is obvious that these methods will give different results, and that the best method is the one which most faithfully reflects the arterial CO_2 pressure. Continuous fractional sampling has been shown by Collier *et al.* (1955) to give a reliable indication of the arterial CO_2 pressure. I have applied the method of continuous fractional sampling to the respired gases during anæsthesia with a circle absorber. The sample is drawn from the expiratory tube, at a point just on the patient's side of the soda lime canister, and led for analysis to a CO_2 analyser mounted on the anæsthetic apparatus. The CO_2 analyser I use is the Carbovisor devised by Brinkman and Lamberts (1952) (Fig. 1). The sample is

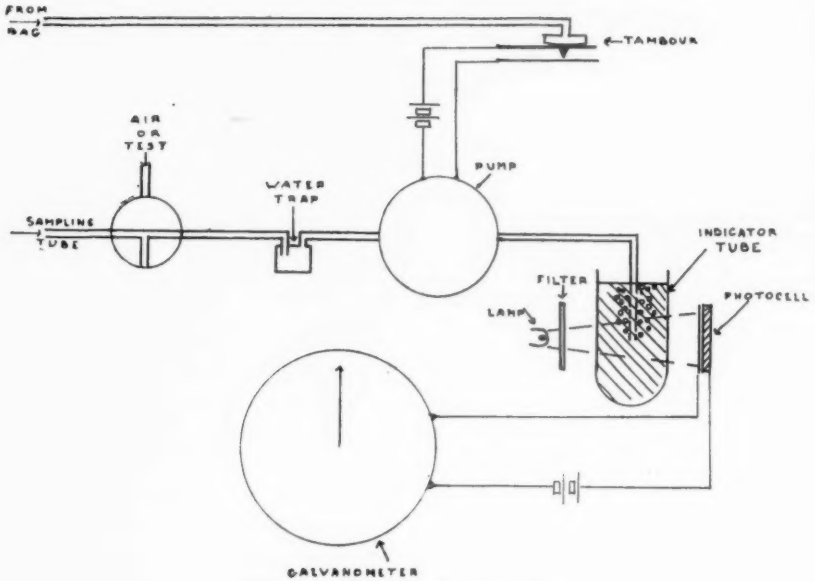

FIG. 1.—Carbovisor (diagrammatic).

drawn by a small diaphragm pump first through a water trap and then through a tube containing a solution of bromthymol blue. It emerges into the tube in very fine bubbles, and frothing is minimized by silicone treatment. CO_2 present in the sample dissolves in the solution and forms carbonic acid. This lowers the pH of the solution, and causes the indicator to change from blue towards green. A beam of light, suitably filtered, shines through the tube on to a photocell. The colour change which takes place with increasing concentrations of CO_2 allows more energy to fall on the photocell, and this increase is indicated by the galvanometer to which it is connected. With a suitable design the relationship between CO_2 concentration and galvanometer deflection is linear over the range 0 to 14%, so that the galvanometer scale can be calibrated directly in CO_2 percentage. A

tambour actuated by changes in the pressure in the system during different parts of the respiratory cycle can be made to operate a relay which starts and stops the pump. In this way sampling can be confined to selected portions of the cycle. Any changes in the intensity of the light source are automatically compensated for by a second photocell, connected in opposition (not shown in Fig. 1). The instrument is fairly compact, and it is seen in position on a standard anæsthetic machine in the photograph (Fig. 2). On the right is

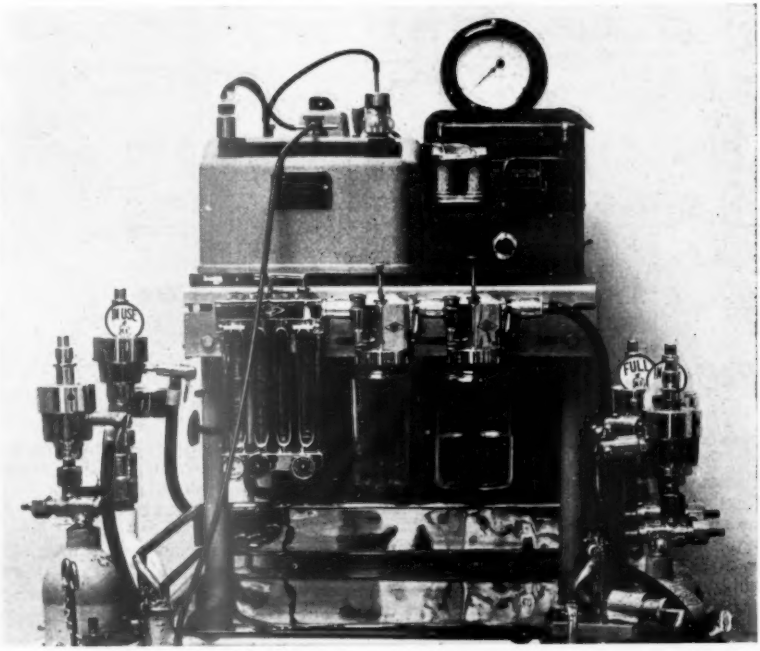

FIG. 2.—Carbovisor and oxygen analyser.

a Pauling paramagnetic oxygen analyser and the anaeroid manometer above gives an indication of the intrapulmonary pressures. The sample is taken to the analyser by a tube leading from the expiratory side of the circuit, proximal to the absorber (Fig. 3).

During expiration, the dead air which leads the advancing column of expired gases first passes the sampling point, and makes a small contribution to the sample. Air from the lungs then follows and is continuously sampled as it moves through the tube during expiration.

During the expiratory pause, and the subsequent inspiration, sampling may continue, and the sample withdrawn during this time consists of the end-expiratory air remaining in the tube between the patient and the canister. This is fairly close to alveolar air. The sample presented to the analyser has been slightly diluted by dead air, which passes quickly past the sampling tube. It is more significantly diluted by that portion of the fresh gases which is carried into the expiratory tube during expiration. The extent of this dilution naturally varies with the flow of fresh gases, but it can be calculated fairly accurately. Moreover, if desired, it can be reduced to vanishing point by interposing another one-way valve in the inspiratory tube near the facepiece (A in Fig. 3), which remains closed during the greater part of expiration. With this valve in use the inlet for fresh gases is transferred to the bag side of the one-way valve (B). Since the response time of this analysing system is measured in minutes rather than fractions of a second, variations during a single respiratory cycle are not indicated, and the instrument measures the mean level of CO_2 in the expired air. During sampling the expiratory valve is kept closed, and the flow of fresh gases is limited to that which will just maintain a constant mean volume in the bag. If the machine is well maintained and there is a gas-tight connexion between it and the patient, this flow need not be more than 400 ml./min., so that we are approaching true closed anæsthesia.

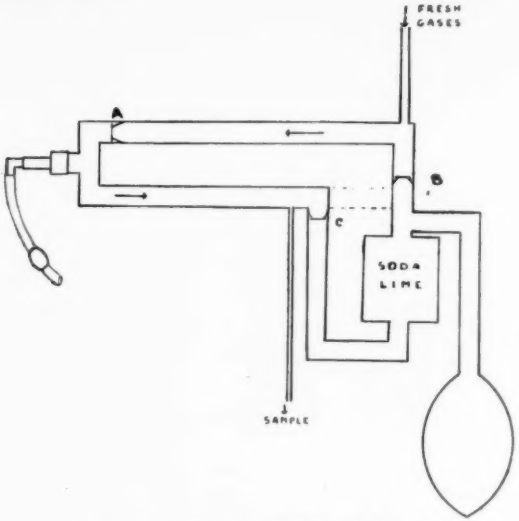

FIG. 3.—Arrangement of closed circuit.

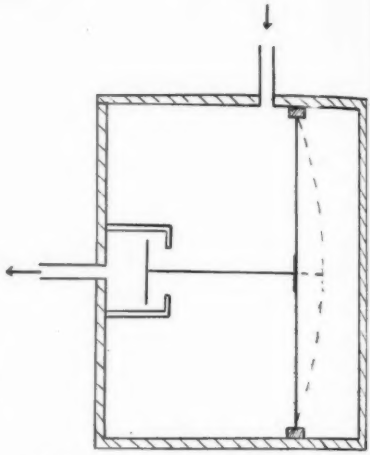

FIG. 4.—Pressure-operated check-valve.

In these conditions the sample presented to the analyser is close to alveolar air, and its CO_2 content is found to agree fairly well with the value calculated from the CO_2 pressure of simultaneously-drawn arterial blood.

When positive pressure respiration is being used the flow of fresh gases has to be higher, for no system is gas-tight in these circumstances, and a flow of 1,000 to 1,500 ml./min. may be required. As long as this does not gain direct access to the sampling tube it will not cause a serious error. To minimize reflux of gases, during positive pressure, through a possibly incompetent valve (C) at the canister inlet which would allow CO_2-free gas to dilute the sample, an additional valve of special design may be interposed in the sampling tube (Fig. 4). This contains a flexible diaphragm linked to a metal disc. The distortion of the diaphragm induced by positive pressure forces the disc against an annular seating and thus closes the sampling line as long as positive pressure is maintained. This may be used instead of the tambour and relay, which is noisy in operation. This arrangement of the analysing system gives one a good idea of the alveolar CO_2 concentration, and hence of the pressure of CO_2 in the arterial blood.

Measurements of the CO_2 in the *inspired* air can also be carried out; and this is the obvious thing to do if it is the behaviour of the machine, rather than that of the patient, that one is studying. In a closed circuit with an efficient absorber, and with all the expired gases passing through it, the CO_2 level of the inspired air is uniformly close to zero. When a proportion of the respired air is made to by-pass the absorber, the CO_2 level of the inspired air naturally rises, and it is interesting to follow the changes in it with changing positions of the control valve on the absorber. Fig. 5 shows an example of this. At "O" the absorber was turned off and the CO_2 returned in the inspired air rapidly rose. Then the absorber was brought in by degrees and the CO_2 inspired fell by corresponding steps, to reach zero when all the respired gases were made to pass through the canister.

If the CO_2 in the inspired air is allowed to rise, that in the expired air will rise too, but only after the CO_2 tension in the blood—and hence in the tissues—has reached a higher level.

Experience shows that with the method of sampling described a normal arterial CO_2 pressure in an anæsthetized patient breathing spontaneously is represented by a CO_2 concentration of 4·5 to 5·5% as registered by the analyser. When positive pressure artificial respiration is being used on the other hand—and particularly if the anæsthetist cannot see the meters—values of 2% to 3% are commonly found. Such low figures can be produced, in the normal subject, only by vigorous forced hyperventilation, and it therefore seems that most anæsthetists overventilate when using positive pressure artificial respiration, and that the pressure of CO_2 in the tissues is thus reduced to an abnormally low level. If it is long continued this may be a serious matter for the body's internal economy, though the resultant ill-effects are subtle and hard to demonstrate. The

most obvious effect, though doubtless not the most important, is on the level of blood pressure, though this is subject to so many other influences that a correspondence between the two can seldom be convincingly demonstrated under clinical conditions.

Fig. 5, however, does show such a correspondence fairly well. As far as could be judged,

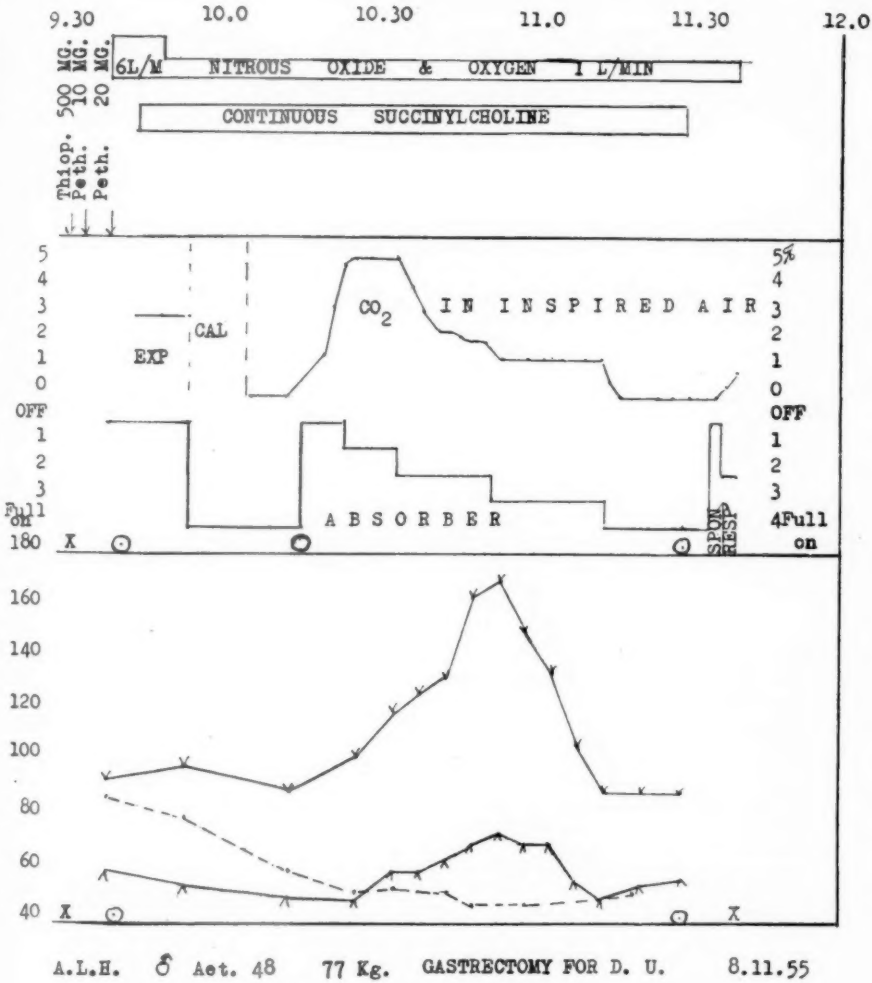

FIG. 5.—Effect of CO_2 level on the blood-pressure level.

the operative stimulus in this case remained constant throughout the relevant period. It is interesting to speculate on the cause of the delay in the cardiovascular response to raised CO_2.

When continuous information of the CO_2 level is available to the anæsthetist, it is not difficult to maintain the arterial CO_2 pressure within normal limits, and it seems to me that this is clearly desirable, even though the ill-effects of departure from it may not be obvious. The level may be prevented from falling too low, in the paralysed patient, either by reducing the minute volume of ventilation below that commonly imposed, or by allowing a fraction of the expired air to return unpurged to the lungs. The first method would seem the more physiological.

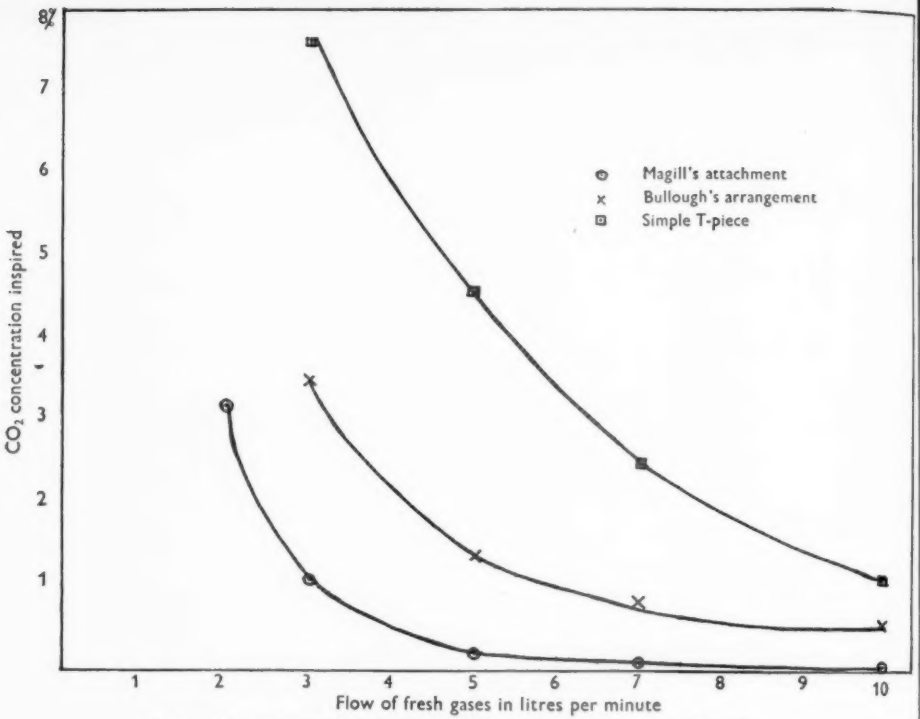

FIG. 6.—Co_2 concentration in the inspired air with various flows of fresh gases for each of the three systems.

So far, I have discussed only closed systems. It is only in such systems that a close correspondence can be expected, with the method of sampling described, between the arterial CO_2 pressure and the sample presented to the analyser. With semi-open methods, in which fresh gases are introduced into the system at about 8 l./min., measurement is complicated by dilution, and instruments with a response time of a fraction of a second are more appropriate, if continuous analysis is to be used. The infra-red analyser is capable of such rapidity, but the difficulties of applying it to the anæsthetized patient are formidable.

Whether one is studying the behaviour of apparatus or the behaviour of the patient, it is important to eliminate as many variables as possible. The variable which is hardest to control is, of course, the response of the patient; and it is difficult to make a useful study of CO_2 accumulation in apparatus unless this variable is done away with. It is therefore not only permissible, but may be necessary, in studies of this kind, to use an artificial or mechanical patient whose behaviour can be kept constant. Studies of this sort are sometimes criticized as being divorced from reality, but if they are well designed they can give more reliable information than work under purely clinical conditions can ever do.

Dr. Bracken has used an artificial patient for some of his work, as did Lind and I in a similar study (Woolmer and Lind, 1954), the results of which are summarized in Fig. 6. These agree with the reasoning of Molyneux and Pask (1951) and with the results of Bracken and Sanderson (1955). All confirm the impression that a flow of fresh gases of 8 l./min. or more is required in a semi-closed system, to avoid returning CO_2 to the patient.

The more important question, however, is what is happening to the patient's arterial CO_2 pressure; and it seems that circumstances may often arise, with bag squeezing of ordinary vigour, in which some re-circulation of CO_2 would prevent too great a lowering of the arterial CO_2 pressure, and would therefore be beneficial.

The conclusions to be drawn from these considerations are, I fear, not decisive. They do not provide, for the average anæsthetist without expensive gas analysers, a ready guide to the correct volume of ventilation; nor do they give proof that harm is done by departures from it. They do suggest, however, that overventilation, in the paralysed patient, is at

least as common as underventilation, and they indicate the developments in instrumentation which will be required before anæsthetists in general can achieve for their patients the requisite degree of CO_2 homeostasis.

Fig. 6 is reproduced from Woolmer and Lind (1954) by kind permission.

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Dr. R. P. Harbord said that he was trying out the effect of 10% carbon dioxide in oxygen for short periods (one minute), as an antidote to curarization. CO_2 causes the motor end-plates to enlarge (Carey, E. J., 1942, *Amer. J. Path.*, **18**, 237), which would be expected to increase the distance between the muscle receptors, thus making it easier to dislodge quaternary ammonium groups. He found carbon dioxide effective if combined with (1) removing the soda lime, (2) tracheal stimulation by suction catheter, and (3) the use of Prostigmin and atropine.

It was extraordinary how well the normal subject tolerated short periods of CO_2 excess, which probably occurred more than was at present realized during the return of muscle tone after curarization.

Dr. E. J. M. Campbell: It is true that in normal lungs in which the ventilation and blood flow are evenly distributed the alveolar and arterial CO_2 tensions are equal, but in disease they are not equal. In particular, end tidal alveolar samples in patients with chronic lung disease have considerably lower CO_2 tensions than arterial blood. It would be a pity if a great deal of effort were to be used in devising methods of gas-analysis during anæsthesia which would be better employed in examining the arterial blood directly.

Dr. G. E. Hale Enderby: A detailed knowledge of the alveolar carbon dioxide in any particular patient would appear to me to be of rather academic interest. Whilst not denying the theoretical advantages of knowing this in every case, I very much question whether I should use this knowledge to maintain each patient in a state of so-called normality. Indeed, I would go so far as to state that in the large majority of my patients I deliberately employ hyperventilation in an attempt to reduce the alveolar carbon dioxide and the blood carbon dioxide levels. This manœuvre is of great assistance in maintaining a smooth blood pressure level during controlled hypotension, and it is undoubtedly true that should the carbon dioxide level be allowed to rise for any reason, the blood pressure quickly shows a corresponding rise and soon becomes uncontrolled. I have come to consider the control of carbon dioxide of great importance in the control of blood pressure and for this reason alone, apart from many others, I should not wish to maintain it in a state of so-called normality in the anæsthetized patient.

Dr. J. E. Hall: I think this work is fundamentally important in establishing what actual level of CO_2 is presented to the patient under the conditions of practical anæsthesia.

The role of CO_2 is most important, for in experimental work when the acid-base balance of the preparation is changed to the acid side of normal its function is impaired and often the change is irreversible; whilst when the change is to the alkaline side there is little functional change and where there is a change it is readily reversed.

Dr. C. F. Scurr said that a check on the ventilation attained during controlled respiration revealed that minute volumes of 8–12 litres were common. The alveolar ventilation resulting would therefore be approximately double the physiological requirements. Using Dr. Bracken's infra-red analyser, it had been found that the alveolar CO_2 concentration could thus fall to 3–4%, corresponding to a tension of 20–30 mm. During such hyperventilation the skin was often lilac in colour. This was probably due to peripheral stasis

in the capillaries, because inspection of blood in the surgical wound revealed that the oxygen saturation was satisfactory. In one such patient, monitoring alveolar CO_2 levels by the infra-red analyser, CO_2 was added to the inspired gases so that the alveolar CO_2 level was restored to normal, although the minute volume of ventilation remained unchanged. When the normal alveolar CO_2 level was attained the skin became a bright, rosy pink again. Provided the dead space was kept low and CO_2 accumulation in the anæsthetic circuit avoided, the best guide to CO_2 homeostasis would be a simple meter to check the ventilation volume during controlled respiration.

When Arfonad was given a fall in alveolar CO_2 levels was observed. It is suspected that this is due to a fall in cardiac output; this results in an increased arteriovenous CO_2 difference, implying an increase on the venous side of the body stores of CO_2 (a converse situation following administration of adrenaline has been reported: Farhi, L. E., and Rahn, H., 1955, *J. appl. Physiol.*, **7**, 472).

Dr. James Montgomerie said that the respiratory pattern had a considerable influence on any tendency for carbon dioxide to accumulate. If there were a pause after expiration, elimination of carbon dioxide was more efficient.

When the nature of the operation permitted an anæsthetic technique using spontaneous respiration, the resistance of the circuit was also important. He had found a semi-closed circuit in which the bag of the Waters canister was replaced by a standard length of corrugated tube to be satisfactory, and economical.

Dr. Herbert H. Pinkerton had had the privilege of visiting Copenhagen about three years ago towards the end of the poliomyelitis epidemic. It was clear that the tendency, in the many cases which were being treated by manual ventilation, was to overventilate. When he referred the matter to Dr. Lassen, whose work in the epidemic is well known, he was able to confirm that the tension of CO_2 in the blood and alveolar air averaged 25 mm.Hg instead of the normal 40 mm.Hg. This state of affairs was often present for weeks on end without any apparent detriment to the patient's general condition.

Dr. W. N. Rollason said that although much time had been spent in estimating the CO_2 content of the alveolar air and the pH, CO_2 content and pCO_2 of the arterial blood, little interest had been taken in either the central or the peripheral venous blood in relation to ventilation and anæsthesia.

He had estimated the pH, CO_2 content, pCO_2 and CO_2 combining power of the peripheral venous blood, using the same antecubital vein, before and after one to one and a half hours of gross hyperventilation (20 l./min.) in a series of 25 well-relaxed and lightly anæsthetized patients with normal cardio-respiratory systems undergoing partial gastrectomy. The significant finding was an average fall of nearly 10 vol.% in the CO_2 combining power indicating the compensatory role the kidneys play in maintaining CO_2 homeostasis in the tissues. The changes in pH, CO_2 content and pCO_2 were small and inconclusive in spite of the low CO_2 tensions reported in arterial blood following hyperventilation and were presumably due to the compensatory slowing down of the circulation known to occur in the hyperventilated patient and seen in the appearance of the skin. The effectiveness of these compensatory mechanisms was reflected in the excellent clinical post-operative state of these cases.

Prolonged hyperventilation in the conscious subject with poliomyelitis, however, should be avoided as it was subjectively unpleasant and induced the respiratory centre to become attuned to a low CO_2 tension rendering weaning and rehabilitation more difficult.

The discomfort complained of by the poliomyelitis patient when different individuals had taken over the manual ventilation was not so much due to hyperventilation, which had been suggested, as to the absence of a negative phase in the respiratory cycle.

Section of Dermatology

President—Louis Forman, M.D., F.R.C.P

[*November* 17, 1955]

Acrodermatitis Enteropathica.—P. J. Hare, M.R.C.P., and B. E. Schlesinger, O.B.E., F.R.C.P.

S. D., girl aged 5 years 8 months.

Birth weight 8 lb. 2 oz. Breast fed for 7 months. Mixed feeding was introduced with difficulty from 5 months.

The rash developed at 4 months on her buttocks, head and face, spreading to the entire body and becoming infected by 6 months. At this time she developed diarrhœa and intermittent vomiting. A diagnosis of dermatitis herpetiformis had been made and liquor arsenicalis given, which caused dramatic temporary improvement of the skin, but aggravated the diarrhœa and vomiting. No other treatment was effective.

She had recurrent otitis media, treated with antibiotics, from 9–18 months, and oral thrush at 10 months. *Stools showed tryptic activity to* 1/256 *dilution. Candida albicans* was not isolated from the skin.

The skin lesions and digestive symptoms persisted intermittently until 5 years. Her maximum weight was 24 lb. at 18 months.

On examination at 5 years 2 months (when first seen at University College Hospital).—A stunted, wasted child with protuberant abdomen. Intelligence normal. Weight 17½ lb. Alopecia totalis. Ectropion. Perlèche. Chronic paronychia.

The skin showed a generalized eruption, most severe on the extremities and around muco-cutaneous junctions. The lesions consisted of circumscribed erythematous areas with peripheral scaling, some in the early stages showing bulla formation and exudation (Figs. 1 and 2).

Fig. 1.—General aspect at the height of the disease (12.5.55).

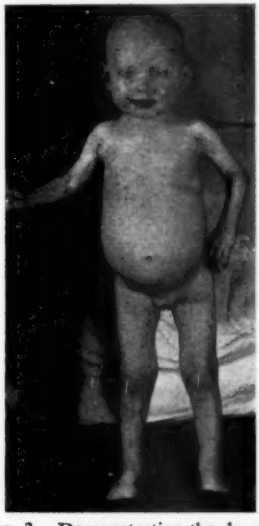

Fig. 3.—Demonstrating the dramatic improvement of the skin after three months' treatment (11.8.55).

Investigations.—Swab from skin: no *Candida albicans*. Swab from mouth: scanty growth of yeast, not *C. albicans*. Stools: Pale, fatty and porridgy or watery: few giardia cysts (none after ten days' treatment with Diodoquin). Total fat 58%: 87% split fat. *No tryptic activity*. Duodenal juice: *no tryptic activity*.

Hb 72%. Serum proteins 5·6 grams/100 ml.; albumin 3·9, globulin 1·7 grams/100 ml.; serum calcium 10·3 mg./100 ml.; plasma inorganic phosphorus 2·2 mg./100 ml.; serum alkaline phosphatase 6·3 K.A. units.

X-ray of skeleton: generalized osteoporosis with several crush fractures of vertebræ.

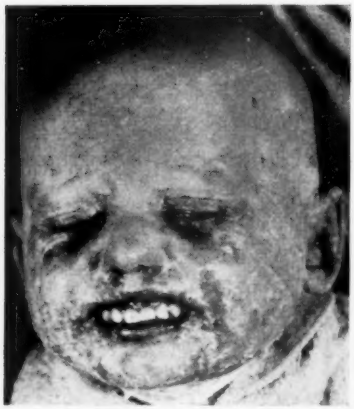

FIG. 2.—Showing severe rash on the face with baldness and loss of eyebrows and lashes (23.5.55).

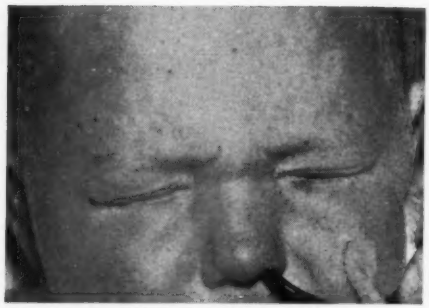

FIG. 4.—Condition on 20.10.55, to show regrowth of lashes, eyebrows and scalp hair.

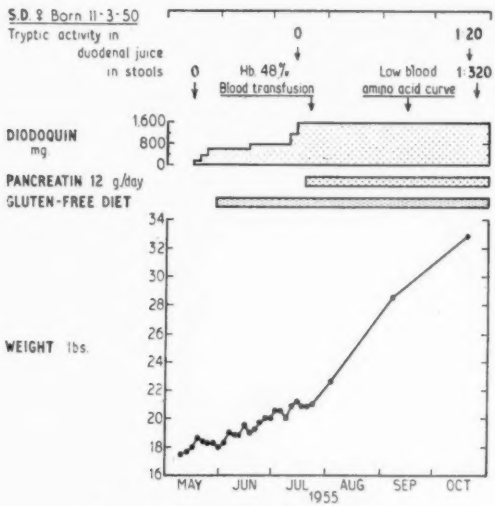

FIG. 5.—Chart of general progress.

Treatment and progress (*see* Fig. 5).—Treatment was commenced with Diodoquin 200 mg. daily, increasing to 1,600 mg. daily by nine weeks. The skin showed little improvement until maximum dosage was reached.

After two weeks, a gluten-free diet was introduced. There was a gradual increase in body weight and decrease in number of stools.

After ten weeks' treatment, pancreatin 12 grams daily was added. At this time a blood transfusion of 1 pint was given because the hæmoglobin had fallen to 48%. There followed a more rapid increase in weight and dramatic clearing of the skin lesions (Fig. 3). After one month's treatment with 1,600 mg. of Diodoquin daily, hair and eyelashes began to appear (Fig. 4). After three months she fell and fractured the right femur, which healed satisfactorily. At four months a blood amino-acid curve after ingestion of casein was low.

After five months' total treatment, her weight was 33 lb., the skin was healed, and she had no ectropion, with eyelashes appearing, an inch growth of hair (Fig. 4) and almost normal nails. Duodenal juice showed *tryptic activity at* 1 *in* 20 *dilution only*. Stools (after three days off pancreatin) *showed tryptic activity to* 1/320 *dilution.*

Dr. Bernard Schlesinger: Acting on the experience of others, Diodoquin was the first treatment we adopted for this little girl. She had an initial dose of 200 mg. a day. As there was little improvement the amount was increased to 1,600 mg. a day. Prior to this, however, the gastro-intestinal disorder had been investigated, as I had been struck with the similarity of the alimentary disturbances with those of cœliac disease and fibrocystic disease of the pancreas. The possible association of one or other of these conditions was further suggested when the fat content of the stools was discovered to be high—a total 58%, of which 87% was split. At the time the child was too ill to carry out further diagnostic tests for cœliac disease, such as a blood sugar curve. Certainly some disturbance of pancreatic secretion seemed to have developed at the height of the disease when the child was 5 years old, as no tryptic activity was found in the stools or duodenal juice at that time. It seems more probable that this disorder was acquired rather than congenital, since trypsin was present in the stools to a dilution of 1 in 256 at the age of 10 months, and has now returned to normal (1 in 320), although it has still not reached the normal range usually found in duodenal juice at this age.

A high dose of Diodoquin produced some improvement, but the skin lesions had not completely healed and the alimentary symptoms remained unabated. Final cure only occurred when a gluten-free diet was offered and pancreatin was given in 3-gram doses before the four main daily meals, the second measure apparently having the greater effect.

Ugland (1952) first described fibrocystic pancreatic changes in acrodermatitis enteropathica, but post-mortem revealed no comparable pathology in other organs, such as is found in "mucoviscidosis", with its widespread primary lesions affecting secreting tissue in various regions of the body. Atrophy of the pancreas secondary to the general wasting would seem to be a much more likely explanation, and this has been described in other marasmic states, such as kwashiorkor in several tropical countries where the diet is poor. The return of pancreatic enzyme secretion, which occurred with the nutritional recovery of the child, is certainly a point in favour of this idea, although it would not explain the simultaneous onset of gastro-intestinal and skin manifestations generally seen in these cases.

In the differential diagnosis, epidermolysis bullosa and skin conditions associated with some porphyrin metabolic disorder have to be considered, but can be excluded for various reasons. A local and generalized monilia infection had repeatedly been suggested as an ætiological factor, but never convincingly demonstrated. In our case candida (not *C. albicans*) was present in a mouth swab on one occasion, but rapidly disappeared without any specific treatment, never to return. The essential cause of the disease still remains unknown. The clinical course of the present case does, however, seem to have advanced our knowledge in regard to treatment. Relapses or persistence of gastro-intestinal symptoms in several cases reported in the past might have been due to insufficient attention to the alimentary aspect of the disorder. Under such circumstances, it would appear to be advisable to examine the stools and duodenal juice for the presence of trypsin, and if it is reduced or absent, to administer pancreatin in addition to Diodoquin, which has already conclusively proved its value. Whether or not a gluten-free diet is also to be recommended during the most active phase of the disease must await further trial.

REFERENCE

UGLAND, J. (1952) *Acta pædiat., Stockh.*, **41**, 483.

Dr. G. B. Dowling: Perhaps some members who saw the case presented by Dr. Hodgsonones (1955) at one of these meetings, would like to hear about his progress. He was admitted to the Goldie Leigh Hospital some eighteen months ago and at the time of admission it seemed that he might not survive, although the diarrhœa had ceased. Hitherto he had been treated with Diodoquin without much noticeable benefit, but the dose was stepped up by degrees to 600 mg. four times daily and on this the skin cleared in the course of some months. Other symptoms, photophobia and protuberant belly especially, also righted themselves very gradually, and the hair and nails regrew fully; he became in fact quite a healthy child. One feature of the condition was an enormous appetite and this he maintained even when apparently quite well. Treatment was stopped

recently as a preliminary step towards returning him to his parents. Within a fortnight he passed some loose stools, he became somewhat sickly and the impetigo-like eruption on the face returned. He began to recover from these symptoms within a week of resuming treatment with Diodoquin and he has finally been sent home under that treatment.

REFERENCE

HODGSON-JONES, I. S. (1955) *Brit. J. Derm.*, **67**, 222.

Dr. B. Solomons: I saw a case of this condition recently, which was similar in nearly all respects to this one. The baby, an 8-month-old boy, was treated with Diodoquin, but as soon as a dosage of 800 mg. per day was reached, the most intense and generalized urticaria appeared, and subsequently œdema of the glottis developed, which was considered to be due to the drug. Several days later the baby died, more probably due to the disease rather than the treatment.

No evidence of monilia was found in my case.

Dr. G. C. Wells: In the case reported by Dillaha *et al.* (1953) monilia was found in the skin lesions at first, but local treatment was successful in eliminating it. After this fresh skin lesions continued to appear until Diodoquin was given. It was our impression that the monilia was a secondary invader.

REFERENCE

DILLAHA, C. J., LORINCZ, A. L., and AAVIK, O. R. (1953) *J. Amer. med. Ass.*, **152**, 509.

Pyodermia Gangrenosum.—STEPHEN GOLD, M.D., M.R.C.P.

V. B., male. At the age of 20 he sprained his ankle and subsequently suffered continuous pain on walking. At the age of 28 he developed pains in the hands as well, and a diagnosis of rheumatoid arthritis was made. He was given simple treatment and later was referred to the skin department with a vesicular eczema of the hands thought to be the result of wax baths. In 1942 he was admitted for in-patient treatment for the rheumatoid arthritis and while he was in hospital he developed a mild and transient iritis in the right eye. At this time the joints involved were the ankles, fingers and wrists, while the elbows and shoulders were spared. X-rays of the hands and wrists revealed several separate cystic areas in the metacarpals and carpals suggesting sarcoidosis but histology of tissue lining one of these cysts showed simple granulation tissue. From 1946 to 1949 he remained well, though in 1948 he had a relapse of the eczema of the fingers and hands. In 1952 he was again being treated for the rheumatoid arthritis and once more the use of wax baths appeared to cause a recurrence of the eczema of his fingers and hands; it cleared with simple treatment. In 1953 the arthritis was still troublesome and he was investigated for a chronic nasal infection thought to be sinusitis—the findings were inconclusive. At this stage Butazolidin was given and it produced symptomatic relief.

In March 1954 he developed a carbuncle on the thigh associated with enlargement of inguinal glands and was treated with penicillin; then followed a succession of boils and carbuncles and by May 1954 he had had fifteen. He was admitted to the Barnet General Hospital and was treated with courses of penicillin and later of chlortetracycline. Boils continued to develop and the staphylococci recovered from the pus were then found to be resistant to both penicillin and chlortetracycline. At this period the behaviour of the boils altered; now, instead of resolving in the normal way they discharged pus and did not heal but extended to form an ulcer. These ulcers spread rapidly and were very painful. They discharged a sero-sanguineous fluid; the edges were undermined, livid and raised, producing by extension a margin that was often polycyclic. There was a surrounding erythema. Pressure on the edge produced a serous fluid from the underlying tissues. These ulcers all showed the same rapid extension and then the slow but sure healing. They all start in the same way, like a boil which breaks down becoming painful and rapidly extending. The base of the ulcer is composed of granulation tissue covered with a thin film of adherent purulent material. They never penetrate deeper than the skin. He has had these ulcers on the shoulders, buttocks, thighs and calves but the great majority have been on the shins and calves. When they heal they leave bizarre-shaped superficial scars. Several ulcers have been 6 in. in diameter but most of them are smaller.

Investigations.—All bacteriological studies have revealed a *Staphylococcus pyogenes* which has now become resistant to all known antibiotics. Occasionally proteus and on one or two occasions a hæmolytic streptococcus have also been found. Staphylococci were recovered from the depth of an unruptured early nodule.

There are but few other abnormal findings. The various blood tests associated with rheumatoid arthritis are positive, there is some increase in the globulin fraction of the serum proteins. Histological study of one early skin papule before it had broken down revealed an acute inflammatory process composed predominantly of polymorphs extending into the subcutaneous tissue. Gram stain shows clumps of Gram-positive cocci in the superficial parts of the abscess but none in the deeper. There was no vascular lesion which could have been a primary process.

Treatment.—He has had courses of all known antibiotics and innumerable local applications without effect. In January 1955 he was given staphylococcal toxoid injections at three-day intervals and the dose gradually increased. After six weeks the injections had to be stopped because of severe pain in the active ulcers, which would last for two days following the injections; finally, one ulcer appeared to become more active following the injection. By March 30 the ulcers were behaving well and he developed for the first time for some months a boil which behaved and resolved like an ordinary one. However, by May 25 further ulcers occurred. In July a carbuncle on the left forearm started to behave as a normal carbuncle but half-way through the healing process broke down, ulcerated and extended as had the previous lesions.

Cortisone was started in October, the initial dose being 200 mg. daily and then reduced to 150 mg. daily. The immediate effect was to produce complete disappearance of pain from the two active ulcers and disappearance of itching in all the scars of previous ulcers. There was a flattening of the edges and he no longer had to change the dressings frequently as the surface became dry. After two or three weeks these ulcers had not in any way extended nor had they healed dramatically. There had been a marked improvement of his rheumatoid arthritis and his general condition is the best it has been for many years, he is still being maintained on cortisone and the active ulcer at the moment appears to be healing satisfactorily.

POSTSCRIPT.—The ulcer had completely healed by the end of November when cortisone was stopped. It has remained healed and since then he has developed one or two ordinary boils. He was seen in April 1956 having had one more ulcer which cleared after two weeks' oral cortisone in February, since when his skin has remained free.

Dr. P. J. Hare: I have had two cases closely similar to this one. Both had rheumatoid arthritis which was mild in one case and fairly severe in the other. In the first case we made strenuous efforts to discover whether the ulcers were due to an infection. Cultures from the surface of the ulcers yielded different organisms on various occasions, but treatment with antibiotics to which the relevant organisms were sensitive failed to help. Cultures made from a washed biopsy and from material aspirated from below the ulcer margin failed to grow any significant organisms and no anaerobic bacteria were demonstrated.

The ulcers in both cases responded dramatically to ACTH but both patients became mentally deranged. In the second case, after ACTH was abandoned, 2·5% hydrocortisone ointment was applied and the ulcers continued to heal.

REFERENCE.—HARE, P. J. (1955) *Trans. St. John's Hosp. derm. Soc. Lond.*, **35**, 31.

Stomatitis for Diagnosis.—R. G. HOWELL, M.R.C.P. (for G. B. MITCHELL-HEGGS, O.B.E., F.R.C.P.).

Mr. J. B., aged 48.

For twenty years he has suffered from soreness of the mouth. This began insidiously at the same time that he developed widespread seborrhœic dermatitis, of which there have been mild recurrences. Angular stomatitis has been present for eighteen months.

Previous history.—Recurrent tonsillitis in childhood. Chronic diarrhœa for one year at age of 11. 1933: Tonsillectomy. 1939: Right maxillary antrum drainage.

On examination.—General physical examination shows no abnormality. There are no skin lesions. The tongue, anterior to the circumvallate papillæ, is smooth and irregular, with superficial ulceration in the mid-line. The mucosa of the cheeks is smooth and red, particularly along the line of closure of the teeth. There are marked angular fissures with crusting. There are numerous gold and amalgam tooth fillings.

Investigations.—Hb 110%. M.C.D. 7·4μ. W.B.C. 7,000; normal differential count. E.S.R. 6 mm. in the first hour (Westergren). W.R. and Kahn negative. Plasma proteins: total 6·7: albumin 4·7, globulin 2·0 grams/100 ml.

X-rays.—Sinuses: A little mucosal thickening in the frontal sinus group; definite mucosal thickening in the right maxillary antrum. Chest: No abnormality. Teeth: Carious cavities in the central incisors.

Scraping from tongue: No fungus seen. Normal mixed salivary flora. Patch test with 1/1,000 mercury perchloride: Negative. Biopsy of tongue: This shows pseudo-epitheliomatous hyperplasia of the epidermis, with no evidence of malignancy. There is a chronic inflammatory infiltrate, mostly of lymphocytes and plasma cells. The appearances are non-specific.

Comment.—The picture is that of a completely non-specific stomatitis. The possibility of electro-galvanic currents between tooth fillings being causative has been considered, but Sir Wilfred Fish, Consultant Dental Surgeon to St. Mary's Hospital, states that these currents can always be demonstrated between fillings of different metals, so that their existence appears to be irrelevant.

Dr. B. C. Tate: I saw a case like this many years ago; it was severe but of shorter duration. She was seen by an Ear, Nose and Throat surgeon who was also a Dental Surgeon. He said two kinds of metal fillings in the teeth were responsible as they were producing electrical charges. He persuaded her to have them drilled out and only one type of filling put in and the condition cleared up completely.

Dr. H. R. Vickers: I remember a patient with a stainless steel denture and amalgam fillings who had severe stomatitis; when the fillings were removed the condition cleared. This patient has a lot of filled teeth and I should have thought the best thing to do would be to remove the metal from his mouth. In some places the gold filling seemed to be on top of the amalgam and if I had had that trouble for all this time I should be prepared to have my teeth out altogether to try and get rid of it.

Scleroderma.—M. FEIWEL, M.R.C.P., and C. D. CALNAN, M.B.

I. F., woman, aged 49.

History.—February 1955: First seen with an eruption of large reddish papules (0·5–1 cm. diam.) with some overlying telangiectasia on each. The papules were only slightly infiltrated and were sparsely distributed over the front and inside of the left leg and thigh and over the left side of the abdomen. No symptoms: no urtication. Biopsy 1 was taken at this time.

July 1955: Relatively rapid development of widespread patches of mixed scleroderma and lichen sclerosus, down the front of the left leg and thigh, over the abdomen and pubes, over the left submammary area and posterior axillary fold. The lower abdominal patch spread over the mid-line to the right side. The lower leg lesions in addition showed marginal erythema and pitting œdema, as well as a number of large bullæ (1–3 cm. diam.). The telangiectatic red papules were still present. Biopsy 2 was taken from an œdematous scleroderma patch on the left leg; and biopsy 3 from one of the red papules on the left thigh.

September 1955: The bullæ on the left leg were followed by ulceration and sepsis but have now healed. Bullæ also appeared on the lower abdominal patch and the area now shows ulceration.

Previous history.—Thyroidectomy at age 27 and increase in weight for the past few years.

On examination.—Extensive patches of localized scleroderma, some with hyperkeratosis and features of lichen sclerosus, on left leg, thigh, abdomen, chest and axillary fold. The abdominal lesion is ulcerated. The movements of the left knee are severely limited by the sclerosus. The red papular lesions are no longer present. Liver and spleen not palpable. No adenopathy except in groins as a result of sepsis over the pubic lesion.

Investigations.—Blood count normal. Bleeding time normal. Clotting time 9 min. (normal 2–6 min.). Blood cholesterol 125 mg./100 ml.

Histology (Dr. H. Haber).—*Biopsy* 1 (Left thigh, February 1955): "There is an extraordinary number of mast cells almost in a tumorous fashion surrounding blood vessels. The infiltrate reaches deep down the vascular network giving it probably clinically the appearance of deep-seated nodules."

Biopsy 2 (Left leg, July 1955): "The epidermis is apparently normal. The upper cutis shows extreme lymphœdema as seen in lichen sclerosus et atrophicus, the rest of the cutis is also œdematous and shows an infiltration partly perivascular and partly scattered and consisting chiefly of plasma cells, round cells and a few mast cells."

Biopsy 3 (Left thigh, July 1955): "The collagen stains pale and there is also œdema to be seen. The infiltration is the same as in the first section."

Comment.—This case presents several interesting features:

(1) The unusual telangiectatic red papules consisting of mast cells made the initial diagnosis of urticaria pigmentosa without any clue that scleroderma was to develop.

(2) Considerable pitting œdema in the early stages of the morphœic patches on the legs.

(3) The combination of scleroderma and lichen sclerosus in the same patches, which supports the view that they are part of one process.

(4) The large bullæ which may occur in some cases and have been described previously.

The following cases were also shown:

Yaws.—Dr. DAVID ERSKINE.

Granuloma of the Foot for Diagnosis.—Dr. R. G. HOWELL (for Dr. G. B. MITCHELL-HEGGS).

Eczema of Hands with Lymphœdema.—Dr. C. D. CALNAN (for Dr. G. B. DOWLING).

Sarcoidosis with Involvement of the Lips and Buccal Mucous Membrane.—Dr. ARTHUR ROOK and Dr. R. A. DAVIS.

Case for Diagnosis. ? Blue Nævus.—Dr. J. SAVAGE.

Dermatitis Nodularis Necrotica.—Dr. P. R. MONTGOMERIE (for Dr. E. J. MOYNAHAN).

Acquired Epidermolysis Bullosa.—Dr. P. F. BORRIE.